

# **AUTOMATED INSULIN DELIVERY TO DIABETIC PATIENTS**

BY

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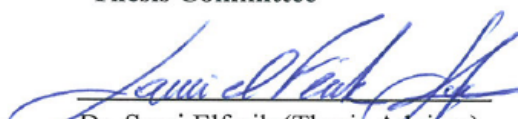
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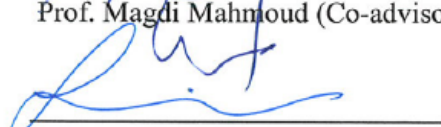
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This thesis, written by **MUSTAFA AL-NASSER** under the direction of his thesis advisor and approved by his thesis committee, has been presented and accepted by the Dean of Graduate Studies, in partial fulfillment of the requirements for the degree of **MASTER OF SCIENCE IN SYSTEMS ENGINEERING**.


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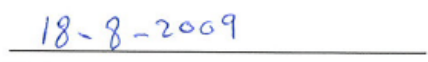
  
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***Dedicated to my Father & Mother***

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## **Abstract:**

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Diabetes is one of the most widely spread diseases in the world nowadays. It can be classified into either Type 1, in which there is almost no insulin production, or Type 2, in which there is insulin production but it is not enough. In order to treat this disease, the researchers are trying to understand the system of glucose–insulin system and to describe its dynamics by using several mathematical models. Ordinary differential equations, integral differential equations, partial differential equations, delay differential equations, and stochastic models are the five main types of most mathematical models. In order to automate insulin delivery to diabetes patients, various control techniques are implemented which can be classified as model- independent (such as optimal control) and non-model independent (such as run to run control). The literature shows the possibility of automating insulin delivery for diabetes patients. However, no method is fully successful due to the complexity of this process, and the number and types of factors involved.

In the present study we are using a two time-delay model. In terms of control, we are using linear matrix inequality tools (LMI) in formulating the control technique which will stabilize the plant (patient) and force it to follow the desired pattern or desired model. The new control technique is simulated on the selected model, and the results are promising to be implementation in reality.

## ملخص الرسالة:

الاسم: مصطفى أحمد الناصر

عنوان الرسالة: أتمتة إيصال الأنسولين إلى مرضى السكر.

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يعتبر مرض السكري أحد أكثر الأمراض شيوعاً في عالمنا اليوم . يصنف العلماء هذا المرض إلى نوعين بناءً على كمية الأنسولين المنتجة في الجسم. النوع الأول الذي لا ينتج فيه البنكرياس أي كمية من الأنسولين ويعتمد فيه المريض كلياً على حقن الأنسولين من الخارج بينما النوع الثاني ينتج البنكرياس الأنسولين ولكن بكمية غير كافية لتنظيم السكر في الدم. لعلاج هذا المرض حاول العلماء فهم عملية تنظيم الجلوكوز في الدم بواسطة الأنسولين وفهمه ديناميكياً هذا النظام باستخدام النماذج الرياضية. هناك خمسة أنواع رئيسية تصنف تحتها معظم النماذج الرياضية : نماذج المعادلات التفاضلية التكاملية , نماذج المعادلات التفاضلية الجزئية , نماذج المعادلات التفاضلية التأخرية , النماذج العشوائية. قام العلماء باستخدام العديد من تقنيات التحكم من أجل أتمتة عملية إيصال الأنسولين إلى الدم لتنظيم مستوى الجلوكوز. تصنف معظم تقنيات التحكم الآلي المستخدمة في علاج هذا المرض بناءً على اعتماديتها على النموذج الرياضي إلى قسمين : تقنيات معتمدة على النموذج الرياضي كتقنية التحكم الأمثل وتقنيات غير معتمدة على النموذج الرياضي كتقنية تحكم دورة إلى دورة. أظهرت الأبحاث والأعمال السابقة إمكانية أتمتة عملية تنظيم مستوى الجلوكوز في الدم باستخدام الأنسولين ولكن لم ينجح أين منها في علاج المشكلة بشكل كامل نظراً لتعقيد هذه العملية وعدد ونوع العوامل المرتبطة بهذا العملية.

في هذا البحث , استخدمنا نموذج رياضي بتأخيرين زمنين لوصف عملية تنظيم الجلوكوز في الدم . واستخدمنا أدوات المتراجحة المصفوفية الخطية لصياغة تقنية التحكم التي تجعل النظام مستقراً وتدفعه لتتبع نمط معين ذو خواص مختارة. قمنا بعمل محاكاة لهذا النظام لاختبار التصميم وأظهرت النتائج إمكانية تطبيق هذا التصميم في علاج مرضى السكر بشكل فعال.

## NOMENCLATURE

$G$  = Blood plasma glucose concentration above basal value.

$I$  = Plasma insulin concentration above basal value.

$X_r$  = Insulin in the remote compartment.

$G_{sc}$  = Glucose concentration on the subcutaneous layer.

$D_m$  = Meal glucose disturbance (mg/dL/min).

$J$  = Objective function.

$P$  = Prediction horizon.

$M$  = Control horizon.

$K$  = Sample time index.

$\Delta u$  = The manipulated input increment.

$\hat{y}$  = The predicted output.

$x(t)$  = State vector.

$u(t)$  = Control input.

$w(t)$  = Disturbance input.

$z(t)$  = Controlled output.

$\tau$  = Constant time delay.

# **CHAPTER 1**

## **DIABETES BACKGROUND**

### **1.1. Introduction**

Diabetes mellitus is a group of metabolic disorders characterized by inability of the pancreas to regulate the blood glucose concentration due to defects in insulin secretion and/or insulin action, the pancreas either does not release insulin or does not properly use insulin to uptake glucose in the plasma [91].

Insulin, the heart of glucose level control, was discovered in 1921. It has been purified and manufactured by recombinant DNA technology. The insulin treatment mimics normal physiology in order to prevent the complications of hyper- and hypoglycemia. The amount of the injected insulin is typically based on the blood glucose level and on the estimated insulin release kinetics from the subcutaneous depot.

Diabetes mellitus is one of the worst diseases with respect to the size of affected population. According to the data published in 2002 by the American Diabetes Association [41, 42] 18.2 million people (about 6.3% of the total US population) had type

2 diabetes. The direct and indirect cost of the treatment of diabetes was 132 billion dollars. The world-wide diabetic population is much higher, especially in underdeveloped countries.

This section gives a medical overview about the diabetes (general terms and idiom), and finally the insulin glucose control in the normal patient.

## **1.2. Classification of Blood Glucose Levels**

According to The Diabetes Control and Complications Trial (DCCT) Research Group [22], blood glucose level has been classified into three main categories: Normoglycemia, Hypoglycemia, and Hyperglycemia.

Normoglycemia is defined as the normal condition with blood glucose concentrations in the range of 70 (3.9 mmol/l) to 110 mg/dl (6.04 mmol/l). Inadequate secretion of insulin by the diabetic pancreas results in poor maintenance of the Normoglycemia with elevated blood glucose concentrations. The only treatment is with subcutaneous or intravenous insulin injections, traditionally administered in an open-loop manner. Without insulin treatment, these patients die.

Hyperglycemia is known to induce insulin resistance and diabetes via increased blood glucose levels [22]. Hyperglycemia is considered when blood glucose exceeds 140 mg/dl (7.8 mmol/l) after an Oral Glucose Tolerance Test, or 100 mg/dl (5.5 mmol/l) after a Fasting Glucose Tolerance Test. DCCT [22] state that the most of the long-term

complications associated with diabetes, such as nephropathy and retinopathy, result from sustained Hyperglycemia. In the United Kingdom Prospective Diabetes Study (UKPDS) [95] only 23% of patients allocated to diet alone attained fasting plasma glucose levels below 140 mg/dl.

The persistent Hyperglycemia in diabetes is associated with long-term complications and dysfunction of various organs, especially the eyes, kidneys, nerves, heart, and blood vessels.

On the other hand, Hypoglycemia will happen when the blood glucose level becomes less than 40 mg/dl (2.2 mmol/l) [49]. This condition is typically caused by the over-delivery of insulin ,and it starves the body cells of fuel Hypoglycemia is a short-term concern but it can lead to insulin shock as well as death.

### **1.3. Types of diabetes**

Medical researchers have classified diabetes mellitus into two types: Type 1 diabetes, or Insulin- Dependent Diabetes Mellitus (IDDM), and Type 2 diabetes, or Non Insulin Dependent Diabetes Mellitus (NIDDM), [(13), (16)].

Type 1 diabetes is characterized by the patient's immune system destroying the insulin- producing  $\beta$ -cells in the pancreas so that exogenous insulin is required to control the disease. This type commonly develops in young people (under 20 years old) and persists throughout life [95]. It may account for 5% to 10% of all diagnosed cases of



diabetes. It is believed that both genetic factors and virus infections cause this type of diabetes. Risk factors for type 1 diabetes include autoimmune, genetic, and environmental factors. DCCT [22] showed that an improved metabolic control was achieved by using intensive insulin treatment in Type 1 diabetes patients.

Even more severe defects in insulin secretion are present in patients with type 1 diabetes following islet transplantation, when Normoglycemia is maintained in the absence of exogenous insulin treatment [13]. This suggests that glucose homeostasis can be maintained despite significant loss of  $\beta$ -cell function when an individual has normal insulin sensitivity.

Type 2 diabetes has been associated with defects in components of both the short-term and chronic negative feedback loops [11]. Type 2 diabetes is a heterogeneous disorder characterized by insulin resistance and insulin deficiency due to a deficit in the mass of  $\beta$  cells, reduced insulin secretion, and resistance to the action of insulin [1]. The relative contribution and interaction of these defects in the pathogenesis of this disease remains to be clarified. About 90% to 95% of all diabetics are diagnosed with type 2 diabetes. This type of diabetes is associated with older age, obesity, family history of diabetes, prior history of gestational diabetes, impaired glucose tolerance, physical inactivity, and race/ethnicity [10]. African Americans, Hispanic/Latino Americans, Native Americans, some Asian Americans, Native Hawaiian, and other Pacific Islanders, are at particularly high risk for type 2 diabetes. Type 2 diabetes is increasingly being

diagnosed in children and adolescents [10]. About 150 million individuals are estimated to have type 2 diabetes worldwide [1].

Insulin-stimulated glucose disposal is reduced by 50-100% in patients with type 2 diabetes as compared to non-diabetic controls. However, insulin resistance of a similar magnitude has been documented in many non-diabetic individuals including obese subjects, or during pregnancy, puberty, and aging [11]. Thus, Normoglycemia can be maintained in subjects with insulin resistance via increases in blood insulin levels. Defects of insulin secretion have been demonstrated in some people with type 2 diabetes [12].

It was observed that the  $\beta$ -cell mass is reduced by 40-50% in patients with type 2 diabetes when compared with weight-matched non-diabetic subjects [13]. In comparison, approximately 80-90% of the  $\beta$ -cell mass is lost before the onset of hyperglycemia in individuals who develop type 1 diabetes, suggesting that a greater  $\beta$ -cell mass is required in the presence of insulin resistance. This is consistent with the observation of a 43% higher  $\beta$ -cell mass in Normoglycemia subjects with insulin resistance due to obesity.

Although these data suggest that multiple defects are required for the onset of type 2 diabetes, it is unclear if these defects have a single causal origin or if they occur independently. Experimental induction of insulin resistance by using either high fat feeding, glucocorticoid administration, or genetically induced obesity has been shown to cause type 2 diabetes under certain circumstances. This supports the hypothesis that insulin resistance can cause  $\beta$ -cell defects, and hence diabetes, either by overworking the

$\beta$ -cells or by toxic effects of hyperglycemia on the  $\beta$ -cells. However, the existence of Normoglycemia in humans and animals highly resistant to insulin suggests that independent defects in insulin sensitivity and  $\beta$ -cell function are required for type 2 diabetes [13].

Moreover, in Type 1 and Type 2 diabetes, some women can have glucose intolerance that is diagnosed during pregnancy. These types are common among obese women and women with a family history of diabetes. Gestational diabetes requires treatment during pregnancy period to normalize the maternal blood glucose levels to avoid complications in the infant. After pregnancy, 5% to 10% of women with gestational diabetes are found to have type 2 diabetes. Between 20% to 50% chance of developing diabetes in the next 5-10 years can happen with women who have had gestational diabetes [9].

Other specific types of diabetes result from specific genetic conditions (such as maturity-onset diabetes of youth), surgery, drugs, malnutrition, infections, and other illnesses. Such types of diabetes may account for 1% to 5% of all diagnosed cases [9].

DCCT and UKPDS [95] demonstrated that tight glucose control reduces the risk of long term complications of type 1 and type 2 diabetes, thus reducing the cost to the health care system. There is no threshold for the relationship between blood glucose, Glycosylated Hemoglobin (HbA1C), and reduced risk. This indicates that glucose levels in subjects with type 1 or type 2 diabetes should be as close as possible to Normoglycemia.

It is estimated that nearly 50% subjects with type 2 diabetes will receive insulin at some stage of their disease [49].

## **1.4. Insulin Control**

The normal physiologic insulin secretion has two profiles:

- 1) The basal secretion provides a background rate of insulin to the body.
- 2) The meal related bolus secretion controls glucose level after having meals.

The variables that indicate the basal insulin needs for an individual include growth and development, hormonal status, age, gender, stress levels, health status, and activity level. In addition, the amount and composition of food dictate the meal related needs [66].

According to the present review surveys, the optimum treatment strategies for insulin treatment are used for type 1 diabetes. Insulin titration, or optimum insulin dosing, is a difficult task but is at the cornerstone of the management of type 1 diabetes [95]. DCCT has shown that intensive insulin therapy leads to improved outcomes of blood glucose control. On the other hand, DCCT showed that resources needed to achieve this goal are beyond the present means. Novel approaches are needed to assist patients with type 1 diabetes and healthcare professionals in achieving the goals set by the DCCT. Information technology has an important role to play in contributing to these activities [21].

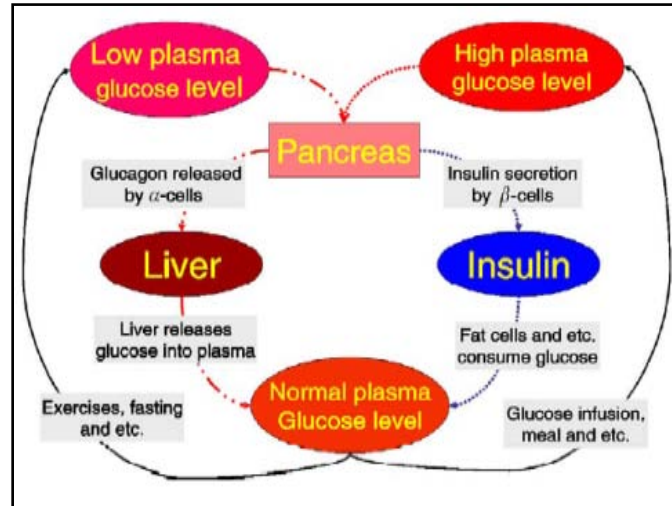
Treatment of type 2 diabetes has received little attention from the adaptive control community except when titrating insulin dosing [95]. This may need revision given the complexities associated with the management of type 2 diabetes. It is usual to start the treatment of type 2 diabetes with non-pharmacological therapies. The base effort of these therapies is to improve glycaemic control and to begin the process of helping patients to make healthy life-style changes. Modification of the nutrition is the first step. If treatment goals are not achieved after a trial of dietary and life-style changes, an oral hypoglycemic is prescribed alone or in combination with insulin [21].

Even minor glucose elevations increase the risk of complications [24]. DCCT was the landmark study of 1440 type 1 diabetic people randomized into two treatment groups: intensive insulin delivery and standard care. Those people who had mean blood glucose concentrations below 110 mg/dl had no increase risk for retinopathy, nephropathy and peripheral vascular disease. Those patients with high glucose hemoglobin levels had a significant and positive correlation with increased risk [21]. However, when the blood glucose concentration was normalized, the risk of severe life-threatening hypoglycemia increased up to 10- fold above the risk in those patients with hyperglycemia. Thus the goal of achieving and maintaining normal blood glucose includes accepting the risk of hypoglycemia. A recent long-term study by the DCCT group has confirmed these conclusions.

## 1.5. Glucose Control in Healthy Individuals

In the healthy individuals, the counter-regulatory hormone glucagon would be released in response to hypoglycemia to raise blood glucose concentration. However, the counter-regulatory response in the diabetic patient is often blunted or absent, and hence it is less effective [90]. The exogenous factors that can affect the blood glucose concentration include food intake, rate of digestion, exercise, and reproductive state. It is therefore important to regulate diabetic patients' blood glucose concentrations to keep them within the Normoglycemia limits.

As shown in Figure 1, the normal pancreas has two phases of insulin delivery: a first phase consisting of an immediate bolus and a second phase of prolonged insulin delivery [(49), (90)]. The function of the first phase is reduce the glucagon secretion from the pancreatic  $\alpha$  cell and thus turn off the hepatic output of glucose, while the function of the second phase of insulin secretion is to metabolize the slower acting carbohydrates. The normal  $\beta$  cell has its first priority to prevent hyperglycemia. Thus the  $\alpha$  cells are needed to secrete glucagon to prevent late postprandial hypoglycemia [90]. In summary, insulin and glucagon are secreted from  $\beta$  cells and  $\alpha$  cells respectively.



**Figure 1.1: Physiological glucose insulin regulatory system. [8]**

When the blood glucose concentration level is high, the  $\beta$  cells release insulin, which lowers the blood glucose concentration level by inducing the uptake of the excess glucose by the liver and other cells such as muscles, and by inhibiting hepatic glucose production [8]. The only way the  $\beta$  cell can respond to a falling blood glucose concentration is to turn off the insulin secretion. There is no way the  $\beta$  cell can retract the insulin once it is given.

When the blood glucose level is low, the  $\alpha$  cells release glucagon, which results in increasing the blood glucose level by acting on liver cells and causing them to release glucose into the blood [8].

The  $\beta$  cell depends on the other counter-regulation hormones that should be secreted to buffer the falling glucose concentration. The hormones that play a major role in counter-regulation are glucagon, epinephrine, cortisol and growth hormone. This delicate balance is perfectly arranged to maintain the blood glucose within the Normoglycemia range [90].

## **CHAPTER 2**

### **LITERATURE REVIEW**

#### **2.1 Introduction**

In this chapter, we present a survey of the literature on the modeling and control of insulin- glucose regulatory system. We will start by listing different models relevant to our work. The second section will present the different control strategies that have been considered. The advantages and weaknesses of each model will be considered.

#### **2.2 Mathematical Models**

Many mathematical models have been developed to better understand the mechanisms of the glucose insulin regulatory system. These models differ on the way in which they formulate and mimic the process. Each model has its own advantages and drawbacks, and each of them addresses a different aspect of the glucose-insulin



regulatory process. Types of models which have been used in the literature can be classified mathematically as:

- 1- Ordinary differential equations (ODEs).
- 2- Delay differential equations (DDEs).
- 3- Partial differential equations (PDES).
- 4- Stochastic differential equations (SDEs) .
- 5- Integro-differential equations (IDEs).

Different software packages can be used for different types of models for numerical analysis and simulations.

### 2.2.1 Ordinary Differential Equations

- **Bergman Minimal Model**

This model depends on the measurements of the glucose level in the subcutaneous layer, so that the controller can decide and calculate the optimal amount of insulin to inject into the diabetes patient. In fact, several versions are used to model the patient ,and some of them are complex, but the following simplified version of Bergman's widely used Minimal model [73,85,86] has five states:.

$$\frac{dG}{dt} = -P_1(G + G_b) - X_r G + D_m(t)$$

$$\frac{dX_r}{dt} = -P_2 X_r + P_3 (I - I_b)$$

$$\frac{dI}{dt} = -nI + \frac{U(t)}{V_I} \quad (2.1)$$

$$\frac{dG_{sc}}{dt} = \frac{G - G_{sc}}{5} - R_{utln}$$

$$\frac{dD_m}{dt} = -\alpha D_m(t)$$

$$x = \begin{bmatrix} G \\ X_r \\ I \\ G_{sc} \\ D_m \end{bmatrix} \Rightarrow \dot{x} = \begin{bmatrix} \dot{G} \\ \dot{X}_r \\ \dot{I} \\ \dot{G}_{sc} \\ \dot{D}_m \end{bmatrix}$$

The system at the steady-state point is:

$$x_s = \begin{bmatrix} G_b \\ X_{br} \\ I_b \\ G_{bsc} \\ D_{bm} \end{bmatrix}, \quad u_s = nI_b V_I, \quad d_s = 0$$

A very brief description of the five states;

G: Blood plasma glucose concentration above basal value (mg/dL).

Xr: Insulin in the remote compartment (mU/L).

I (mU/L): Plasma insulin concentration above basal value.

$G_{sc}$ : Glucose concentration on the subcutaneous layer. This state approximates  $G$ , and is the one which are measurable (mg/dL).

$D_m$ : Meal glucose disturbance (mg/dL/min).

The elements in  $x_s$  vector are basal values for the system.

The manipulated insulin infusion rate ( $U(t)$ ; mU/min) is the input to the model. The time variable  $t$  is measured in minutes. The standard parameters which are usually used for the model can be found in Table 1 which denotes the basal values for the system.

**Table 2.1: Bergman model parameters.**

Name	Value
$P_1$	$0.028735 \text{ min}^{-1}$
$P_2$	$0.028335 \text{ min}^{-1}$
$P_3$	$5.035 \cdot 10^{-5} \text{ mU/L}$
$n$	$5/54 \text{ min}^{-1}$
$V_I$	12 L
$R_{utln}$	0.7400mg/dL/min
$\alpha$	0.05
$G_b$	81.3 mg/dL
$X_{br}$	0
$I_b$	15 mU/L
$G_{bsc}$	$G_b - 5R_{utln}$
$D_{bm}$	0

To prevent the patient from going to the hyperglycemia or hypoglycemia level and to keep him or her in the normal situation , input and output constraints are required. Boundaries on the blood sugar level (output constraints) are required as follows:

$$60 \text{ mg/dL} \leq z \leq 180 \text{ mg/dL} \quad (\text{Where } z \text{ is the measured variable}).$$

The input constraints restrict the rate and the variations of possible injected insulin, and so that system can work within physiological and physical limits. The chosen constraints are shown below:

$$0 \text{ mU/min} \leq u \leq 100 \text{ mU/min}$$

$$-16.7 \text{ mU/min} \leq \Delta u \leq 16.7 \text{ mU/min}$$

The system of differential equations can be set up as follows:

$$\dot{X} = \bar{A}X + \bar{B}U + \bar{E}D$$

where X, U and D are incremental variables,  $X = x - x_s$ ,  $U = u - u_s$  and

$$D = d - d_s.$$

where X is the state vector, U is the input variable for insulin injection, and D is the input variable for meal consumption considered as meal disturbance.

The matrices  $\bar{A}, \bar{B}, \bar{E}$  are the partial derivatives of the model:

$$\bar{A} = \begin{bmatrix} -P_1 - X_r & -G_b & 0 & 0 & 1 \\ 0 & -P_2 & P_3 & 0 & 0 \\ 0 & 0 & -n & 0 & 0 \\ 0.2 & 0 & 0 & -0.2 & 0 \\ 0 & 0 & 0 & 0 & -\alpha \end{bmatrix}$$

$$\bar{B} = [0 \quad 0 \quad \frac{1}{V_t} \quad 0 \quad 0]^T$$

$$\bar{E} = [1 \quad 0 \quad 0 \quad 0 \quad -\alpha]^T$$

However, the Bergman minimal model has two main disadvantages:

1. Highly ill-posed inverse problem.
2. Glucose kinetics are mostly reconstructed by deterministic iterative numerical algorithms which might be not accurate.

- **Six-dimensional ODE model**

This model is based on two negative feedback loops which describe the effects of insulin on glucose utilization and production and the effect of glucose on insulin secretion. Sturis et al. (1991) [46] developed a six-dimensional ODE model which is the basis of several DDE models [5, 52, 45, 20].

The model is described by the following system of nonlinear ODE:

$$\frac{dG(t)}{dt} = G_{in} - f_2(G(t)) - f_3(G(t))f_4(I_i(t)) + f_5(x_3(t)),$$

$$\begin{aligned}
\frac{dI_p(t)}{dt} &= f_1(G(t)) - E \left( \frac{I_p(t)}{V_p} - \frac{I_i(t)}{V_p} \right) - \frac{I_p(t)}{t_p} \\
\frac{dI_i(t)}{dt} &= E \left( \frac{I_p(t)}{V_p} - \frac{I_i(t)}{V_p} \right) - \frac{I_i(t)}{t_i} \\
\frac{dx_1(t)}{dt} &= \frac{3}{t_d} (I_p(t) - x_1(t)) \\
\frac{dx_2(t)}{dt} &= \frac{3}{t_d} (x_1(t) - x_2(t)) \\
\frac{dx_3(t)}{dt} &= \frac{3}{t_d} (x_2(t) - x_3(t))
\end{aligned} \tag{2.2}$$

Tolić et al. [44] simplified the previous model by using only linear or up to second-order terms in the Taylor expansions of the functions  $f_1, f_2, f_3, f_4$  &  $f_5$  and they were able to show similar numerical results.

Where

$$f_1(G) = R_m / (1 + \exp((C_1 - G/V_g)/a_1)) \tag{2.3}$$

is a function which models the production of pancreatic insulin as controlled by the glucose concentration.

$$f_2(G) = U_b (1 - \exp(-G/(C_2 V_g))), \tag{2.4}$$

is a function for glucose utilization by brain and nerves.

$$f_3(G) = G/(C_3 V_g); \quad (2.5)$$

$$f_4(I) = U_0 + (U_m - U_0)/(1 + \exp(-\beta \ln(I/C_4(1/V_i + 1(Et_i$$

$f_3(G(t))f_4(I(t))$  stands for insulin-dependent utilization/uptake by muscle, fat cells and others. This insulin-dependent glucose utilization is accomplished by the so-called “remote insulin”.

$$f_5(I) = R_g/(1 + \exp(\alpha(I/V_p - C_5))) \quad (2.7)$$

is a function modeling hepatic glucose production. Table 2.2 lists the different parameters in the model and their nominal values.

**Table 2.2: Functions parameters values**

Parameters	Units	Values	Parameters	Units	Values
$V_g$	1	10	$U_0$	mg. min <sup>-1</sup>	40
$R_m$	$\mu\text{Umin}^{-1}$	210	$U_m$	mg. min <sup>-1</sup>	940
$a_1$	mg.l <sup>-1</sup>	300	$\beta$		1.77
$C_1$	mg.l <sup>-1</sup>	2000	$C_4$	$\mu\text{U l}^{-1}$	80
$U_b$	mg. min <sup>-1</sup>	72	$R_g$	mg. min <sup>-1</sup>	180
$C_2$	mg.l <sup>-1</sup>	144	$\alpha$	$l\mu\text{U l}^{-1}$	0.29
$C_3$	mg.l <sup>-1</sup>	1000	$C_5$	$\mu\text{U l}^{-1}$	26

$t_p$	min	6	E	$1\text{min}^{-1}$	0.2
$t_i$	min	100	$t_d$	min	36
$V_p$	1	3	$V_i$	1	11

This model can be considered generic because it describes various aspects of glucose-insulin regulation. However, this model does not produce self-sustaining oscillation which is a major characteristic of this system [14].

### 2.2.2. Models in the form of integral-differential equations

One of the main reasons to introduce integral-differential models is that the widely used *minimal model* lacks a proper qualitative behavior because its time lag equals the basal glucose level  $G_b$ . De Gaetano and Arino [3, 4] modified the *minimal model* and formulated a delay integro differential equation model which can be considered closer to real representation of the insulin- glucose system:

$$\begin{aligned}\frac{dG(t)}{dt} &= -b_1 G(t) - b_4 I(t) G(t) + b_7 \\ \frac{dI(t)}{dt} &= -b_2 I(t) + \frac{b_6}{b_5} \int_{t-b_5}^t G(s) ds\end{aligned}\tag{2.8}$$

$$G(t) = G_b, t \in [-b_5, 0], G(0) = G_b + b_0, I(0) = I_b + b_3 b_0$$

where :

$t$  is time [ min].



$G$  is the glucose plasma concentration [mg/dl].

$G_b$  is the basal (preinjection) plasma glucose concentration [mg/dl].

$I$  is the insulin plasma concentration.

$I_b$  is the basal (preinjection) insulin plasma concentration [pM].

$b_0$  is the theoretical increase in plasma concentration over basal glucose concentration at time zero after instantaneous administration and redistribution of the IV glucose bolus [mg/dl].

$b_1$  is the spontaneous glucose first order disappearance rate constant [ $\text{min}^{-1}$ ].

$b_2$  is the apparent "1st-order disappearance rate constant for insulin [ $\text{min}^{-1}$ ].

$b_3$  is the 1st-phase insulin concentration increase per (mg/dl) increase in the concentration of glucose at time zero due to the injected bolus [ $\text{pM}/(\text{mg/dl})$ ].

$b_4$  is the constant amount of insulin-dependent glucose disappearance rate constant per pM of plasma insulin concentration [ $\text{min}^{-1} \text{pM}^{-1}$ ].

$b_5$  is a delay that represents the length of the past period whose plasma glucose concentrations influence the current pancreatic insulin secretion [min];

$b_6$  is the constant amount of second-phase insulin release rate per (mg/dl) of average plasma glucose concentration throughout the previous  $b_5$  minutes [ $\text{min}^{-1}$  pM/ (mg/dl)].

$b_7$  is the constant increase in plasma glucose concentration due to constant baseline liver glucose release [(mg/dl)  $\text{min}^{-1}$ ].

This model describes better the Glucose-Insulin system by taking into account the following aspects:

- **Glucose concentration changes in blood depend on:**

- (1) Spontaneous, insulin-independent net glucose tissue uptake.
- (2) Insulin-dependent net glucose tissue uptake, which means that changes in tissue glucose uptake and in liver glucose delivery are considered together.
- (3) Constant baseline liver glucose production.

- **Insulin plasma concentration changes depend on:**

- (1) Spontaneous constant-rate decay because of insulin catabolism,
- (2) Pancreatic insulin secretion.

The second right-hand-side term in  $\frac{dI(t)}{d(t)}$  is a delay term that refers to the pancreatic secretion of insulin. Effective pancreatic secretion (after the liver first-pass effect) at time  $t$  is proportional to the average value of glucose concentration in the  $b_5$  minutes preceding time  $t$ . Because of delay, the glucose level must be specified both at time zero and at times  $[-b_5, 0]$ .

In their attempt to extend this model and to make it more generic Li et al [45] introduced the following changes:

$$\begin{aligned}\frac{dG(t)}{dt} &= -f(G(t)) - g(G(t), I(t)) + b_7 \\ \frac{dI(t)}{dt} &= -p(I(t)) + q(L(G_t))\end{aligned}\tag{2.9}$$

where

$$\begin{aligned}G(0) &= G_b + b_0, I(0) = I_b + b_3 b_0, G(t) = G_b, t \in [-b_5, 0], G_t(\theta) = G(t + \theta), \\ t > 0, \theta &\in [-b_5, 0]\end{aligned}$$

Since this model is generic, so that, J. Li [45]:, define  $L(G_t)$  for two special cases:

**Case I:**

$$L(G_t) = G(t - b_5)\tag{2.10}$$

$$\frac{dG(t)}{dt} = -b_1 G(t) - \frac{b_4 I(t) G(t)}{\alpha G(t) + 1} + b_7\tag{2.11}$$

$$\frac{dI(t)}{dt} = -b_2 I(t) + b_6 G(t - b_5)$$

**Case II:**

$$L(G_t) = \frac{1}{b_5} \int_{-b_5}^0 G(t + \theta) d\theta$$

$$\frac{dG(t)}{dt} = -b_1 G(t) - \frac{b_4 I(t) G(t)}{\alpha G(t) + 1} + b_7 \quad (2.12)$$

$$\frac{dI(t)}{dt} = -b_2 I(t) + \frac{b_6}{b_5} \int_{-b_5}^0 G(t + \theta) d\theta$$

The author (J. Li) assumed that the insulin-dependent glucose uptake follow the Michaelis–Menten form because of a physical constraint which allows a unit of insulin to handle only a limited amount of glucose in a unit of time. Both analysis and numerical simulations are mostly based on the assumption that the insulin dependent net glucose tissue uptake follows Michaelis–Menten dynamics with  $1/\alpha$  as the half-saturation constant.

However, this assumption makes the mass action law in this situation less realistic.

$$\frac{dG(t)}{dt} = \text{Glucose production} - \text{Glucose utilization},$$

$$\frac{dI(t)}{dt} = \text{Insulin production} - \text{Insulin clearance}.$$

To address this issue Mukhopadhyay et al. [6] proposed the following modifications:

$$\frac{dG(t)}{dt} = -b_1 G(t) - b_4 I(t) G(t) + b_7 \quad (2.13)$$

$$\frac{dI(t)}{dt} = -b_2 I(t) + b_6 \int_0^\infty w(s) G(t - s) ds$$

where:  $G(t) = G_b, t \in (-\infty, 0), G(0) = G_b + b_0, I(0) = I_b + b_3 b_0$

$$w(s) = \alpha^2 s e^{-\alpha s} \quad [6].$$

### 2.2.3. Models in the form of partial differential equations

Many models in the form of PDEs exist. For example, Boutayeb and Derouich [2], Boutayeb and Twizell [1], Aslanidi et al. [74], Bertram and Pernarowski [82] (reaction–diffusion type related to the Langerhans islets), Wach et al. [76] are all PDE models. In particular, Wach et al assumed that Injected soluble insulin is present in the subcutaneous tissue in hexametric and diametric form and only diametric molecules can penetrate the capillary membrane:

$$\begin{aligned} \frac{\partial h}{\partial t} &= P(Qd^3 - h) + D\nabla^2 h, \\ \frac{\partial d}{\partial t} &= -P(Qd^3 - h) + D\nabla^2 h - Bd \end{aligned} \quad (2.14)$$

where  $h, d$  are concentrations of hexametric and diametric insulin,  $P$  is a rate constant,  $Q$  is a chemical equilibrium constant,  $D$  is a diffusion constant, and  $B$  is an absorption rate constant. Wach et al solve numerically the system of PDE, and they divided the subcutaneous region into spherical shells for the space discretization.

#### 2.2.4. Models in the form of delay differential equations (DDEs):

These models takes into consideration the effect of time delay in the Insulin –Glucose system allowing DDEs model to mimic the real situation and make them more realistic than the previous models. Several models were formulated in the form of DDEs based on the model by Sturis et al (1991) [46]. One of these models was formulated by K. Engelborghs [52], in which the glucose triggered insulin production delay is ignored:

$$\begin{aligned}\frac{dG(t)}{dt} &= G_{in} - f_2(G(t)) - f_3(G(t))f_4(I(t)) + f_5(I(t - \tau_2)) \\ \frac{dI(t)}{dt} &= f_1(G(t)) - \frac{I(t)}{t_1}\end{aligned}\tag{2.15}$$

However, insulin production stimulated by glucose time delay is missing. We made another trial to model the exogenous insulin infusion by using the same internal insulin production function form which was considered to be too artificial.

$$\begin{aligned}\frac{dG(t)}{dt} &= G_{in} - f_2(G(t)) - f_3(G(t))f_4(I(t)) + f_5(I(t - \tau_2)) \\ \frac{dI(t)}{dt} &= \alpha f_1(G(t)) - \frac{I(t)}{t_1} + (1 - \alpha)f_1(G(t - \tau_1))\end{aligned}\tag{2.16}$$

Li et al. (2005) [49] proposed another model, known as the two time delay model.

It includes time delay in the insulin response to the glucose stimulation:

$$\frac{dG(t)}{dt} = G_{in} - f_2(G(t)) - f_3(G(t))f_4(I(t)) + f_5(I(t - \tau_2)) \quad (2.17)$$

$$\frac{dI(t)}{dt} = f_1(G(t - \tau_1)) - d_i I(t)$$

Where the initial condition  $I(0) = I_0 > 0$ ,  $G(0) = G_0 > 0$ ,  $G(t) \equiv G_0$  for all  $t \in [-\tau_1, 0]$  and  $I(t) \equiv I_0$  for  $t \in [-\tau_2, 0]$  with  $\tau_1, \tau_2 > 0$ .

$\tau_1$  is the time delay of insulin production stimulated by glucose,  $\tau_2$  is the time delay of hepatic glucose production and  $d_i$  is the insulin degradation rate. This model proved to be a possible mechanism to explain the origin of ultradian (recurrent periods or cycles repeated throughout a 24-hour) oscillations in pancreatic insulin secretion.

### 2.2.5. Stochastic Models:

Because of the practical limitations, the new algorithms are developed mainly to analyze the blood glucose level (BGL) time series (TS). This time series is decomposed into a cyclic component to describe the daily pattern and a trend component to express the BGL long term variations.

For treatment with Insulin to be satisfactory, the trend component should be almost constant lies in the normal range, while the cyclic component varies within acceptable limits.

To evaluate the variability BGL standard deviation or the mean amplitude of glycemic excursions (MAGE) may be calculated [25]. However, it is better to use the instantaneous index to describe the variability of BGL.

The stochastic volatility (SV) model was used to capture the randomness of the data. However, the SV model is difficult to estimate because of its nonlinear structure. Nonlinear estimation methods, such as Markov chain Monte Carlo (MCMC) algorithms, solve this problem partially [23]–[33].

Recent research by Paolo Magni (2006) used the SV model literature:

$$y_i = t_i + \sigma_i \epsilon_i, \quad i = 1, \dots, N \quad (2.18)$$

The trend can be described by means of an integrated random walk model:

$$t_i = t_{i-1} + s_{i-1} \quad (2.19)$$

$$s_i = s_{i-1} + w_{i-1}, \quad i = 2, \dots, N \quad (2.20)$$

with  $t_i, s_i$  initial conditions, and where  $w_i$  is the random fluctuation of the trend.

It is more convenient to use the logarithm of volatility since volatility is non-negative,

$h_i = \ln(\sigma_i^2)$ , the stochastic model becomes:

$$h_i = h_{i-1} + u_{i-1}, \quad i = 2, \dots, N \quad (2.21)$$



with  $h_1$  initial condition and where  $u_i$  are the random fluctuations of the log-volatility.

Let us denote  $t = [t_1 \quad \dots \quad t_M]^T$ ,  $z = [t_1 \quad s_1 \quad w_1 \quad \dots \quad w_{N-2}]^T$

$$H_z = \begin{bmatrix} 1 & 0 & 0 & 0 & \dots & 0 \\ 1 & 1 & 0 & 0 & \dots & 0 \\ 1 & 2 & 1 & 0 & \dots & 0 \\ 1 & 3 & 2 & 1 & \dots & 0 \\ \vdots & \vdots & \vdots & \vdots & \ddots & \vdots \\ 1 & N-1 & N-2 & N-3 & \dots & 1 \end{bmatrix}$$

The trend model:

$$t = LH_z z \quad (2.22)$$

where  $L$  is a matrix that takes into account the missing measurement.

$$h = [h_1 \quad \dots \quad h_M]^T, \quad x = [h_1 \quad u_1 \quad w_1 \quad \dots \quad u_{N-1}]^T$$

$$H_x = \begin{bmatrix} 1 & 0 & \dots & 0 \\ 1 & 1 & \dots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 1 & 1 & \dots & 1 \end{bmatrix}$$

The volatility model can be rewritten as:

$$h = LH_x x \quad (2.23)$$

One of the important points of this model is that it uses simultaneous identification techniques to calculate the trend and the volatility instead of known ones. However, this model is valid on a fixed time grid which manages missing data and ignores spot measurement, which may result in underestimating the

variability. The simulation results of this research are promising from a medical point of view.

## **2.3. Control Algorithms**

The challenge of automating insulin delivery for diabetic patients by using implantable pumps and glucose sensors has received considerable attention over the last 10-20 years. Recent surveys and tutorials provide excellent overviews of diabetes control strategies from a control engineering perspectives, some of these techniques are described in the following sections.

### **2.3.1. PID/PD controller**

Several control algorithms have been used since 1960 in medical treatment to inject both glucose and insulin to control the glucose level in the diabetes patient. On-off control and Biostator are examples of these techniques, B.W. Bequette [11]. Several work are using Biostator by (GCIIS), Fabietti PG, Massi Benedetti M-1991[25] ,and later to the “Biostator” algorithm and device of Clemens , Brunetti P, Cobelli C, Cruciani P-1993 [17]. This controller uses a low-volume continuous-flow blood glucose sampling mechanism with a dual infusion system (insulin and dextrose) to maintain blood glucose concentration at the desired value. The control algorithm used was a nonlinear proportional-derivative (PD) structure, using a five-point moving average of glucose measurements to minimize noise effects. However, dual delivery system (insulin & glucose) is

difficult because of reservoir's additional size, and it did not show good results in medical treatment for diabetic patients.

Therefore, researchers considered only insulin injection in their algorithms. They used standard or modified PID control algorithms with some enhancement to the feedback control (such as feed forward action) to compensate for the meal disturbance. The calculation is performed by assuming that the meal time and content are known. However, PD controller was used more often in the previous research and preferred on PID controller to avoid the integral action which may result in insulin overdosing (Wind up) which, in turn, may cause hypoglycemia during and after the meals period.

The windup problem can be overcome or mitigated by using “anti-reset windup” with the integral control action.

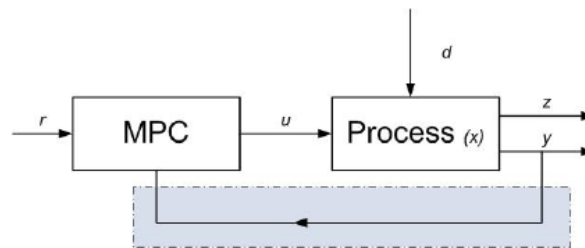
The proposed PID controllers were evaluated in simulation studies of post-prandial responses. A few were evaluated by using applications to dogs or humans in experimental conditions (e.g., intravenous vs. subcutaneous sensors and pumps, different types of insulin and insulin analogs, etc.).

### **2.3.2. Model Predictive Control (MPC):**

A model-based control strategy with model predictive control (MPC) is one of the control algorithms most used in recent years [53]. In fact, MPC is used to treat

diabetes patients for the same reasons that it has been very successful in the process industries:

- (i) It can be used to control both linear and nonlinear processes. So, both linear and nonlinear models can be used.
- (ii) It can handle inherent inequality constraints.
- (iii) It can predict future behavior.
- (iv) Model parameters can be easily updated.



**Figure 2.1: Model Predictive controller (MPC).**

**MPC objective function:**

$$J = \sum_{i=1}^P (r_{k+i} - \hat{y}_{k+i})^2 + \lambda \sum_{i=1}^M \Delta u_{k+i-1}^2 \quad (2.24)$$

where:

J Objective function.

P prediction horizon.

M the control horizon.

K the sample time index.

$\lambda$  Weight on the manipulated input.

$\Delta u$  The manipulated input increment.

$\hat{y}$  The predicted output.

$r$  the desired setpoint.

A key issue is the availability of a dynamic model that is reasonably accurate for the current patient conditions. The evaluations for diabetes control problems using MPC technique have shown that glucose control can be improved in comparison with conventional PID control strategies.

In 1999, Parker et al were the first to publish an MPC approach to manage the glucose levels in type 1 diabetic patients. Their research was a simulation study that used the Sorensen (1985) model as the “virtual patient” [84,85]. They used the following approaches to develop the model:

- i. Direct identification from patient data using rich signals.
- ii. Reduced order numerical models derived from the original compartmental model.
- iii. Linearized versions of the compartmental model coupled with a state estimator.

The state estimator was used to estimate unmeasured meal disturbance, providing a form of feed-forward control without the need for direct knowledge of the meal. They also performed online estimation of the key physiologic parameters by using a Kalman filter.

In Parker's simulation studies, the MPC with state estimation showed the following results:

- 1) The meals disturbance can be compensated without the direct knowledge of meal timing and/or content.
- 2) The blood glucose levels were controlled well and they settled within normal range.
- 3) This technique was tested for measurement noise and patient uncertainty (parametric uncertainty) it is also managed, including estimation of key patient parameters.

However, the disadvantage of MPC is that it requires a good model that almost matches the real process in patients. This is a difficult requirement because the model parameters depend, e.g., on the age, weight, health of the patient. So, these parameters differ from patient to patient and they are affected by the patient conditions such as anger, sleep, sport, which are reflected in the glucose level in the blood.

MPC has not been tested in detailed clinical trials involving multiple meals but the system including the pump and controller is used for certain cases only, and the controller and model parameters should be tuned for each patient.

### 2.3.3. Run-to-Run Control:

Run-to-run control is a technique which deals with the systems that show cyclic behavior, K. S. Lee & J. H. Lee, et al [53]. The main idea in this technique is that certain disturbances are persistent across repeated cycles in a process. So, this technique avoids the repetition of corrective action to compensate for such disturbances and it formulates an update on a time scale of the entire cycle which necessitates only one correction at the end of each batch and in each cycle the control action is refined more until nearly perfect control is achieved. This type of control is also called iterative learning control (ILC) which minimizes the effect of the persistent disturbance over multiple cycles.

The control strategy is also based on a measurement, unlike other techniques which are model-based and its independent variable of the control loop is the batch number, as shown in B. Srinivasan, C.J. Primus, et al [9] & C. Owens, H. Zisser [18]. The Run-Run algorithm can be summarized as follows:

1. The input profile is parameterized for  $k$  run,  $u_k(t)$ , as  $U(t, v_k)$ . by considering the  $\psi_k$  as a sample version of the measured output  $y_k(t)$  such that both input parameter vector  $v_k$  and sample output  $\psi_k$  (controlled variable).  
$$\psi_k = F(v_k)$$
2. Choose an initial guess for  $v_k$ ,  $k = 1$ .

3. Complete the run by using the  $u_k(t)$  corresponding to  $v_k$ . Determine  $\psi_k$  from the measurement  $y_k(t)$ .
4. Input parameters are updated by using the following formula

$$v_{k+1} = v_k + K(\psi^\Gamma - \psi_k) \quad (2.25)$$

where:

$K$ : appropriate gain matrix.

$\psi_k$ : The reference value.

Then, set  $k = k + 1$ . And repeat 3, 4 steps until the algorithm converges.

Thus a solution is implemented as an open-loop strategy for each batch (24 hour cycle), and the feedback allows refinement over successive batches (days). The advantage of this technique is that it is almost independent because it translates the limited information about glucose level in the patient into any time of particular interest. In the present context, the limited measurement information of the patient's blood glucose level is translated into quality measurements (max/min glucose) and the resultant quality variables are of the same type of variables that are used to evaluate the effectiveness of a particular insulin regimen.

The results of the clinical trial in H. Zisser, L. Jovanovic, F.J. Doyle III [36], showed that most of the patients responded positively to the algorithm, and the algorithm's predictions were in line with the medical doctors' recommendations.



### 2.3.4. Pole Placement Strategy:

During an oral glucose load, the relationship between plasma insulin and blood glucose concentration in a normal subject has been described by the following proportional derivative control law:

$$I(t) = aG(t) + b \frac{dG(t)}{dt} + c \quad (2.26)$$

where

$I$  is the plasma insulin concentration;

$G$  is the blood glucose concentration;

$a$ ,  $b$ , and  $c$  are the parameters responsible for insulin secretion.

Hashiguchi Y, Sakakida-1994 [38] have estimated the parameter values by using the nonlinear least squares method. Figure 3 illustrate the medical explanation of the subcutaneous-injected insulin by the three-compartment linear model of:

$$\frac{dX(t)}{dt} = IIR(t) - lX(t) \quad (2.27)$$

$$\frac{dY(t)}{dt} = lX(t) - (p + o)Y(t) \quad (2.28)$$

$$\frac{dZ(t)}{dt} = pY(t) - nZ(t) \quad (2.29)$$

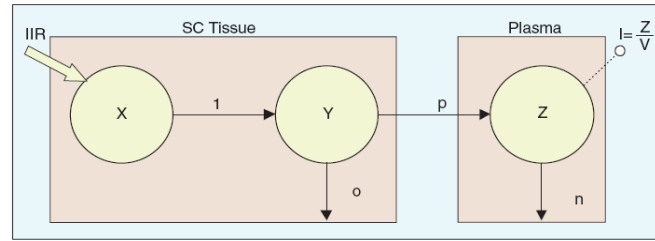
$$I(t) = \frac{Z(t)}{V} \quad (2.30)$$

where

$IIR$  is the insulin infusion rate.

$X$ ,  $Y$ , and  $Z$  are the insulin masses in the two subcutaneous compartments and in plasma, respectively;

$V$  is plasma volume.



**Figure 2.3: The compartmental model of SC insulin absorption and kinetics for pole placement strategy.**

with data obtained in ten diabetic subjects treated with both regular and Lispro insulin, the model parameters have been estimated by nonlinear least squares. The requirement is to have the plasma insulin concentration of the diabetic subject to follows the same dynamics of the normal subject. This control law is obtained by substituting equation 2.26 into equation 2.27, and neglecting higher order derivatives such that:

$$IIR(t) = K_p G(t) + K_d \frac{dG(t)}{dt} + K_c \quad (2.31)$$

where

$$K_p = \frac{amnV}{p}$$

$$\frac{K_d}{K_p} = \frac{1}{l} + \frac{1}{m} + \frac{1}{n} + \frac{b}{a}$$

$$K_c = d + \frac{c}{a} K_p$$

$$m = o + p,$$

$d$  accounts for the IV (intravenous) basal infusion rate.

This system has been tested in VIVO (venous input venous output) on ten type-1 diabetic hospitalized patients both in response to a 75g oral glucose load and to a standard meal. Three therapeutic regimens were employed:

- 1 Regular insulin-injected SC,
- 2 Lispro-injected SC,
- 3 Regular insulin- injected IV.

The obtained results using the IV regular insulin were similar to those achieved with the SC Lispro, with the only statistical difference being plasma insulin concentration values were higher in the SC case. On the other hand, the results obtained by injecting SC regular insulin were significantly worse than that by IV:

- (1) The total dose of insulin was significantly in SC is higher than IV,

(2) And plasma insulin concentrations were lower (30 min) and higher (90 – 300 min), with consequent presence of hyperglycemic peaks followed by hypoglycemic episodes.

The pole-assignment strategy proved to be not robust and requires an iterative assessment of the model parameters, which is difficult to have in clinical practice.

### 2.3.5. Optimal Control:

The optimal control techniques implemented in diabetes treatment used linear diabetic patient model and a quadratic performance criterion (cost function), Swan (1982) [98] solved the glucose control problem for the optimal insulin infusion rate.

$$J_1(u) = \int_0^{\infty} [x_1^2(t) + \rho u^2(t)] dt \quad (2.32)$$

This approach combine optimal control theory and solution of a nonlinear algebraic Riccati equation, and it refines the results of Kikuchi [56, 57], who solved the problem using an approximate solution to the Riccati equation. Kikuchi focused on the initially hyperglycemic diabetic patient and excluded meal disturbance attenuation. After that, Fisher and Teo [27] applied the optimal techniques to control patient blood glucose but they took into consideration both meal consumption and initial hyperglycemia. The performance measure used is:

$$J = \int_0^T x_1^2 dt \quad (2.33)$$

where  $T = 240$  min.

The objective of optimal infusion protocols is to minimize the sum-squared of glucose tracking error. Impulse control (a single injection at time = 0 min) given by:

$$u(t) = \begin{cases} u_0/t_b & \text{if } 0 \leq t \leq t_b \\ 0 & \text{if } t > t_b \end{cases} \quad (2.34)$$

where  $t_b$  is the time taken for the injection and  $u_0$  is the total amount of insulin injected.

It showed superior control in both cases, with perfect reference tracking achievable if a good estimate of the meal was available under the assumption that the rate at which the glucose enters the blood  $p(t)$  takes the following form:

$$p(t) = \begin{cases} B & \text{if } 0 < t < t_a \\ B \exp(-\beta(t - t_a)) & \text{if } t \geq t_a \end{cases} \quad (2.35)$$

Where  $B, \beta, t_a$  are constant.

However, this form was found not be practical one because this rate differ from patient to patient. To overcome this problem, Lim and Teo [65] added fuzzy model parameters enhancement to compensate for patient uncertainty. These techniques were tested for the chosen uncertainty set and it proved to be robust and numerically stable.

Also, optimal control was applied by using the “minimal model” of Bergman, et al. [85, 86] in two studies. The first one was done by Ollerton [75], who utilized concept of an integral-squared error (ISE) cost function based on deviation from

the desired glucose value by using sampling times of 10 min and 180 min. Although the longer sampling time was less sensitive to noise about the basal state, Ollerton discretized the “minimal model” in 10 min sampling time because as the sampling time increases, the rise time also increases which might miss significant disturbance. This controller showed physiologically unrealistic profiles and high amplitude oscillation because it was sensitive to oscillation of the glucose profile about the basal state.

An insensitive model was proposed to overcome sensitivity problem, most likely based on a type of dead-band control. Fisher [28] conducted another study by using the same “minimal model,” and an ISE-based objective function.

$$J(u) = \int_0^T G^2(t)dt \quad (2.36)$$

Subject to the constraint

$$0 \leq u(t) \leq u_{max} \text{ for all } t \in [0, T]$$

His cost criterion had two objectives:

- 1) Minimize deviations in glucose concentration from a reference value  
(**Primary objective**).
- 2) Minimize the amount of insulin used for the corrective action  
(**Secondary objective**).

The study tested three insulin infusion profiles, in which the cost function for an initially hyperglycemic patient was minimized by determining that an initial injection plus optimal hourly infusion. However, this algorithm was not robust to patient uncertainty, and because it has a long sampling time (180 min) it missed some important disturbances (fast or inter-sample disturbances).

### **2.2.6. Robust Control ( $H_\infty$ )**

Robust control techniques with  $H_\infty$  criteria was implemented by Kienitz and Yoneyama [53] using a low-order model containing patient-dependent parameters on the following assumptions.

- (1) The main controller was constructed based on a nominal patient model,
- (2) Because of the variations between the patients (parameter variations), the set of frequency-dependent weighting functions was tuned to capture the entire expected patient population. So the controller managed the glucose level in the patient within this range of variation.

This controller can sustain meal disturbance for the nominal patients which is a worthwhile improvement compared to the previous controllers. However, the controller is robust to a small range of variation and it requires to be retuned outside this range.

### 2.3.6. Self-Tuning Adaptive Control:

Glucose level in a diabetic person and its response to insulin depends on several factors such as insulin time sensitivity varies during the day, and the fitness and health of the individual. Because of that, adaptive control is an attractive technique to automate insulin delivery and to compensate for the patient variation and unknown conditions.

There are several papers published on using adaptive control for diabetes problem. In fact, most of the used adaptive techniques were summarized in a review paper by Hovorka in 2004[91], for both type-1 and type-2 diabetes. He considers strategies for two types of situations:

- a. Infrequent glucose measurements are available (e.g., four to seven measurements per day).
- b. Frequent glucose measurements are available (e.g., every five minutes).

The work of Shimoda [97], is an important example of a successful use of the SC route for the closed loop control of insulin-dependent diabetic patients. The reason is mainly the use of Lispro insulin, which is better suited for SC closed-loop control than regular insulin, since it behaves like IV-injected insulin. In fact, the strength of adaptive techniques is that it does not need to re-assess the patient parameters periodically, and so there is no need to retune controller parameters. These techniques were tested by several authors and showed good results



compared to standard techniques such as pole placement. The feasibility of these techniques was shown by Candas and Radziuk [19], & Brunetti [17], in a closed-loop system based on SC Lispro injections and SC measurements. The adaptive strategies which were based on a self-tuning minimum variance controller were conducted by Fisher [29], and improved by Brunetti & Fabietti [26]. This technique represents the glucose-insulin system by the following discrete-time model  $M$ :

$$G_k = M(G_{k-1}, \dots, G_{k-h}, ID_{k-p}, \Theta) \quad (2.37)$$

where:

- (1)  $G_k$  is blood glucose concentration at time  $k$ ,
- (2)  $ID_k$  is insulin dose at time  $k$ ,
- (3)  $\Theta$  is a set of unknown parameters, with  $h$  and  $p$  known time delays.

The recursive techniques were used to estimate the parameter at each time  $k$ , on the basis of  $G_k$  measurement, which provide a prediction horizon of a one-step-ahead,  $G_{k+1}$ , which can be utilized in the on-line regulator design. In fact, the choice of the next dose,  $ID_{k+1}$ , is done so as to minimize a suitable cost function,  $J$ , which in the case of a minimum variance controller is:

$$J_k = (G_{k+1} - G_b)^2 - rID_{k+1}^2 \quad (2.38)$$

where :

$G_b$  is the set point.

$r$  is a weighting factor that penalizes insulin dosage.

thus compromising between the amount of infused insulin and hyper/hypoglycemia. One can assume, like in Fabietti [26], Candas [19] & Fisher[29], that  $M$  is linear, so that both the recursive estimation and the minimization problem can be solved in closed form. Given the adaptive capability of the algorithm, the choice of a linear model with time-varying parameters seems appropriate.

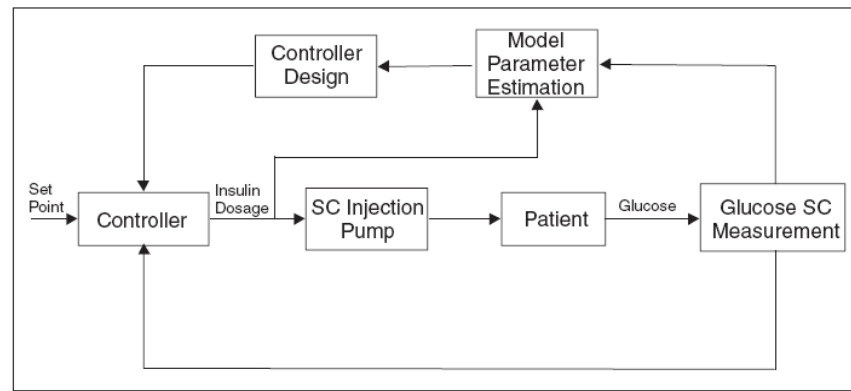


Figure 2.4: Self Tuning Adaptive control block diagram.[80]

### 2.3.7. Nonlinear Predictive Control:

Nonlinear predictive control was proposed by Trajanoski et al. [76,99] to manage the glucose level in patients with the subcutaneous (SC) route.

The keys points of this technique are as follows:

1. It performs several control actions that minimize a certain cost function within a selected time horizon.

2. This cost function does not depend on the control actions to predict the controlled variables but it utilizes an appropriate model for prediction.
3. The control policy is refined by shifting the time window used for the cost function calculation at each sampling time.

The methodology of this technique is similar to that used in adaptive control.

However, there two main differences:

- The selected model in adaptive techniques could be the same for the entire time window, and it does not require to be modified, unlike the one used in nonlinear techniques.
- On the other hand, the control policy requires recalculation, since the optimization problem to be solved changes in accordance with the progressive shifts of the time window.

In other words, instead of model parameter estimation of a nonlinear predictor in Fig. 4, the model used to predict future blood glucose levels is nonlinear and autoregressive (NARX):

$$G_k = f(x_k) + e_k = f(G_{k-1}, \dots, G_{k-n_y}, ID_{k-1}, \dots, ID_{k-n_y}) \quad (2.39)$$

**where**

$G_k$  is blood glucose concentration at time  $k$ ,

$ID_k$  insulin dose at time  $k$ ,

$n_y$  and  $n_u$  are the maximum lags for  $G_k$  and  $ID_k$ , respectively

$$x_k = [G_{K-1}, \dots, G_{K-n_y}, ID_{k-1}, \dots, ID_{k-n_u}]^T$$

The nonlinear function  $f$  can be selected by using the neural network technique, as follows

$$f(x(t)) = \sum_{i=1}^n w_i H(\|x - x_i^0\|) \quad (2.40)$$

where  $H$  is a continuous function from  $\mathbf{R}^{n_y + n_u} \rightarrow \mathbf{R}$ ,  $\| \cdot \|$  is the Euclidean norm,

$x_i^0$  are the  $n$ -centers of the RBFs.

In [13],  $H$  was assumed as:

$$H(\|x - x_i^0\|) = \frac{1}{((x - x_i^0)^2 + \beta)^2} \quad (2.41)$$

where  $\beta$  is a dispersion parameter.

The control input (i.e., the SC insulin infusion rate) corresponds to the solution of the minimization problem:

$$\arg \min_{ID} J = \sum_{j=N_1}^{N_p} [(e_j^T \Gamma e_j) + \sum_{j=0}^{N_c-1} (\Delta ID^T(t+j) \Gamma_u \Delta ID^T(t+j))] \quad (2.42)$$

$$ID = [ID_k, ID_{k-1}, \dots, ID_{k-N_c-1}]^T$$

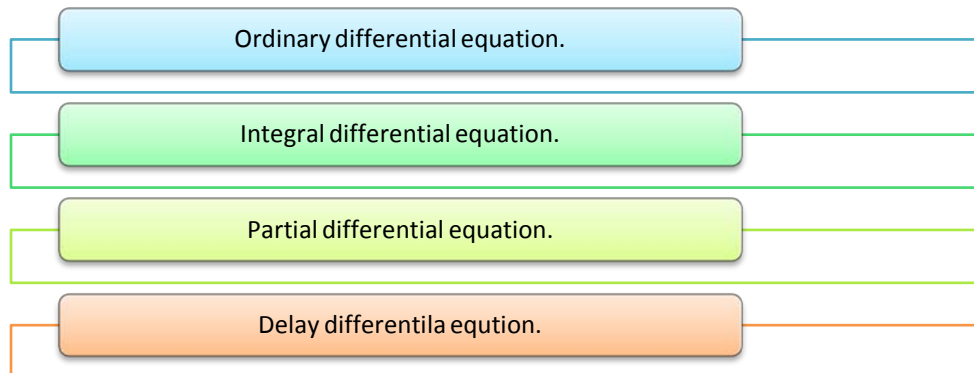
$N_c$ ,  $N_p$ ,  $N_1$ ,  $\Gamma_e$ ,  $\Gamma_u$  are tuning parameters of the controller, selected by trial and error.

The predictive control was tested and showed flexibility in managing blood glucose, even if there is disturbances and parameter variations (i.e., variations in the time constants of the system). In fact, the adoption of this proposed controller to treat diabetic patients is promising.

However, under the presence of meals and lack of in-vivo validation hampers, the results were not good enough to adapt this technique to the patients.

## 2.4. Conclusion

Several mathematical models were formulated to describe and mimic the actual process, in the glucose –insulin system in the human body. These models can be classified according to the mathematical form in which they are formulated. The main forms are:



None of these models is able to fully describe the actual process and each of them has its advantages and weakness.

In this study, we select from the previous model, the time delay model type because:

- a. Using the time delay model is more realistic in physiology, because the glucose- insulin system has significant time delays which cannot be ignored.
- b. The two time delay model (2.17) has the two main significant time delays in the system which is required to describe the real situation correctly. Also, it conforms with physiological characteristics as shown both analytically and numerically

Also, various control algorithms were used and tested to treat diabetes patients. Most of these control techniques are model-dependent, such as model predictive control. Some techniques are model-independent such as run-run control techniques. Optimal, robust and adaptive and run-run control, model independent type, are the most attractive techniques because they can sustain parameters variations, which is always the case in actual process. Moreover, they can handle meal disturbance which was one of main obstacles in earlier treatment trials.

In this study, we will use the LMI technique with  $H_\infty$  criteria to stabilize the glucose-insulin system. Also, we will develop a controller (with the same technique and criteria) which is stabilizing the plant (glucose-insulin system) and track a model with the desired performance characteristics at the same time.

## CHAPTER 3

### TWO TIME DELAY MODEL

#### 3.1. Model Description

The selected DDE (delay differential equation) model has two explicit time delays and describes the glucose–insulin endocrine metabolic regulatory system. The reason for introducing these two time delays is that the insulin secretion by  $\beta$  cell in the liver to manage glucose concentration in the bloodstream or the plasma takes about 5-15 minutes, depending on different individuals. So, to make the model more realistic and precise, these two delays must be introduced in the model. The two time delays are:

(1) The effect of glucose concentration level on insulin secretion time delay  $\tau_1$  due to the complex electro-chemical reactions when the rising glucose concentration level triggers the  $\beta$  cells to release insulin [52, 100, 50]. The delay  $\tau_1$  can be described as insulin response time delay.

(2) The hepatic glucose production time delay  $\tau_2$ . In fact, this delay is introduced because the process of converting the stored glucose and glycogen into glucose and vice versa is done gradually and it takes some time.

The two time delay DDE model selected is as follows:

$$\frac{dG(t)}{dt} = G_{in} - f_2(G(t)) - f_3(G(t))f_4(I(t)) + f_5(I(t - \tau_2)) \quad (3.1)$$

$$\frac{dI(t)}{dt} = f_1(G(t - \tau_1)) - d_i I(t)$$

where the initial condition  $I(0) = I_0 > 0$ ,  $G(0) = G_0 > 0$ ,  $G(t) \equiv G_0$  for all  $t \in [-\tau_1, 0]$

and  $I(t) \equiv I_0$  for  $t \in [-\tau_2, 0]$  with  $\tau_1, \tau_2 > 0$ .

where:

$$f_1(G) = R_m / (1 + \exp((C_1 - G/V_g)/a_1)), \quad (3.2)$$

$$f_2(G) = U_b(1 - \exp(-G/(C_2 V_g))),$$

$$(3.3)$$

$$f_3(G) = G/(C_3 V_g); \quad (3.4)$$

$$f_4(I) = U_0 + (U_m - U_0) / (1 + \exp(-\beta \ln(I/C_4(1/V_i + I(Et_i))))))$$

$$(3.5)$$

$$f_5(I) = R_g / (1 + \exp(\alpha(I/V_p - C_5))); \quad (3.6)$$



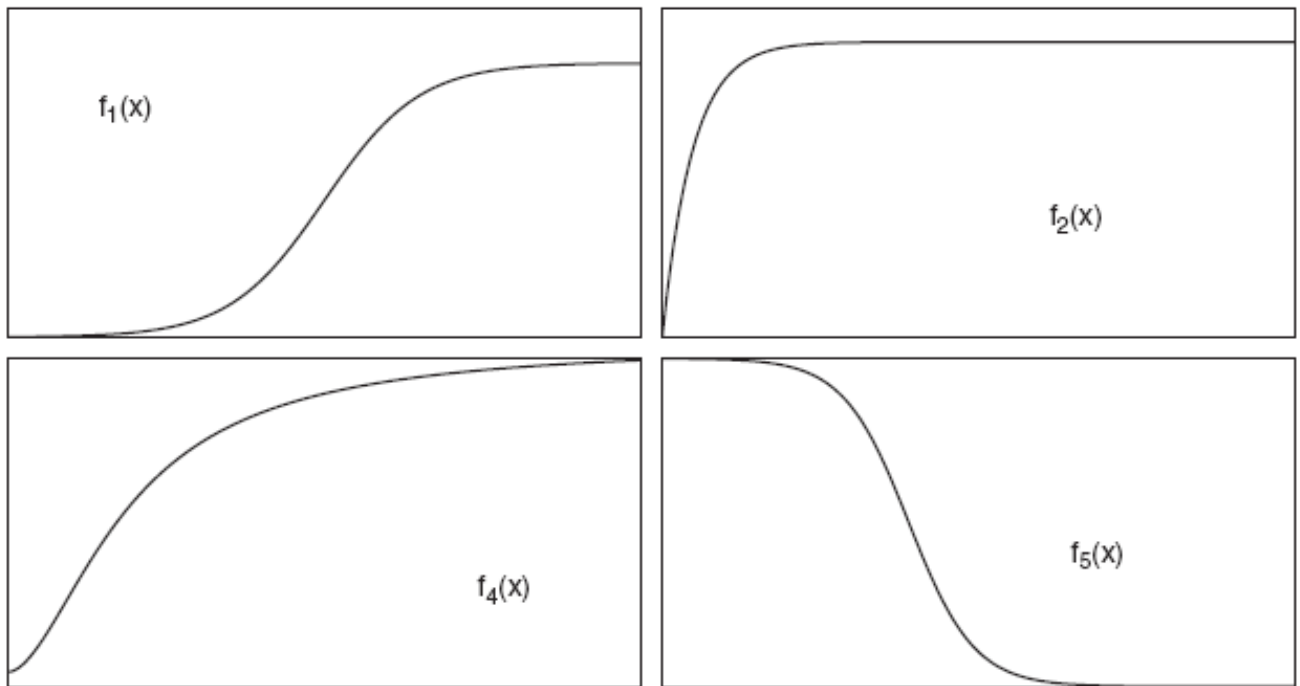
- 1)  $G_{in}$  is due to glucose infusion, e.g., by meal ingestion, oral glucose intake, continuous enteral nutrition or intravenous glucose infusion;
  - 2)  $f_2(G(t))$  stands for insulin independent glucose consumption by the brain, nerve cells and other parts of the body. So, this type of utilization depends on glucose concentration level only.
  - 3)  $f_2(0) = 0, f_2(x) > 0$  and  $f_2'(x) > 0$  are bounded for  $x > 0$  ,  $f_3(G(t))f_4(I(t))$  represents insulin dependent utilization/uptake by muscle, fat cells and others parts of the body. This utilization is accomplished by the so-called “remote insulin”.
- $f_3(x) = k_3x$ , where  $k_3 > 0$  is a constant.  $f_4(0) > 0$  , for  $x > 0, f_4(x) > 0$  and  $f_4'(x) > 0$  are bounded above.  $f_4(I(t))$  is in sigmoidal.
- 4)  $f_5(I(t - \tau_2))$  Indicates hepatic glucose production that is dependent on insulin in the plasma with time delay  $\tau_2 > 0$ . The time delay  $\tau_2 > 0$  reflects that the.  $f_5(0) > 0$  and, for  $x > 0, f_5(x) > 0$  and  $f_5'(x) < 0$ .  $f_5(x)$  and  $|f_5'(x)|$  are bounded above for  $x > 0$ .  $f_5(x)$  is in an inverse sigmoidal shape.
  - 5)  $f_1(I(t - \tau_1))$  stands for insulin secretion from the pancreas. Insulin is stored in  $\beta$ -cell granules. Glucose is the primary stimulus of insulin secretion from  $\beta$  cells. The delay is due to the complex electric processes inside an islet. These processes include glucose molecules that enter islets through Glucose Transporter GLUT2, elevate ATP and then close the  $K^+$  channels. When  $K^+$  channels are closed,  $Ca^{2+}$  channels are open.

- 6)  $d_i I(t)$  stands for insulin degradation and constant  $d_i$  is the degradation rate. The liver and kidney respectively are the primary sites of portal insulin degradation and peripheral insulin clearance. The remaining Insulin which is not cleared by liver and kidney [32] is ultimately removed by other tissues such as muscle and adipose cells.

Table 3.3: Function Parameters values

Parameters	Units	Values	Parameters	Units	Values
$V_g$	1	10	$U_0$	mg. min <sup>-1</sup>	40
$R_m$	$\mu\text{Umin}^{-1}$	210	$U_m$	mg. min <sup>-1</sup>	940
$a_1$	mg. l <sup>-1</sup>	300	$\beta$		1.77
$C_1$	mg. l <sup>-1</sup>	2000	$C_4$	$\mu\text{U l}^{-1}$	80
$U_b$	mg. min <sup>-1</sup>	72	$R_g$	mg. min <sup>-1</sup>	180
$C_2$	mg. l <sup>-1</sup>	144	$\alpha$	$l\mu\text{U l}^{-1}$	0.29
$C_3$	mg. l <sup>-1</sup>	1000	$C_5$	$\mu\text{U l}^{-1}$	26
$t_p$	min	6	E	1 min <sup>-1</sup>	0.2
$t_i$	min	100	$t_d$	min	36
$V_p$	1	3	$V_i$	1	11

By using the same experimental data set which is used in the existing mathematical models such as those in Sturis et al. and Tolic et al. [44,20], the two time delay model confirms most of existing observations of experiments and models, and it shows more robustness, and better agreement with physiological data.



**Figure 3.5: Functions Shapes.**

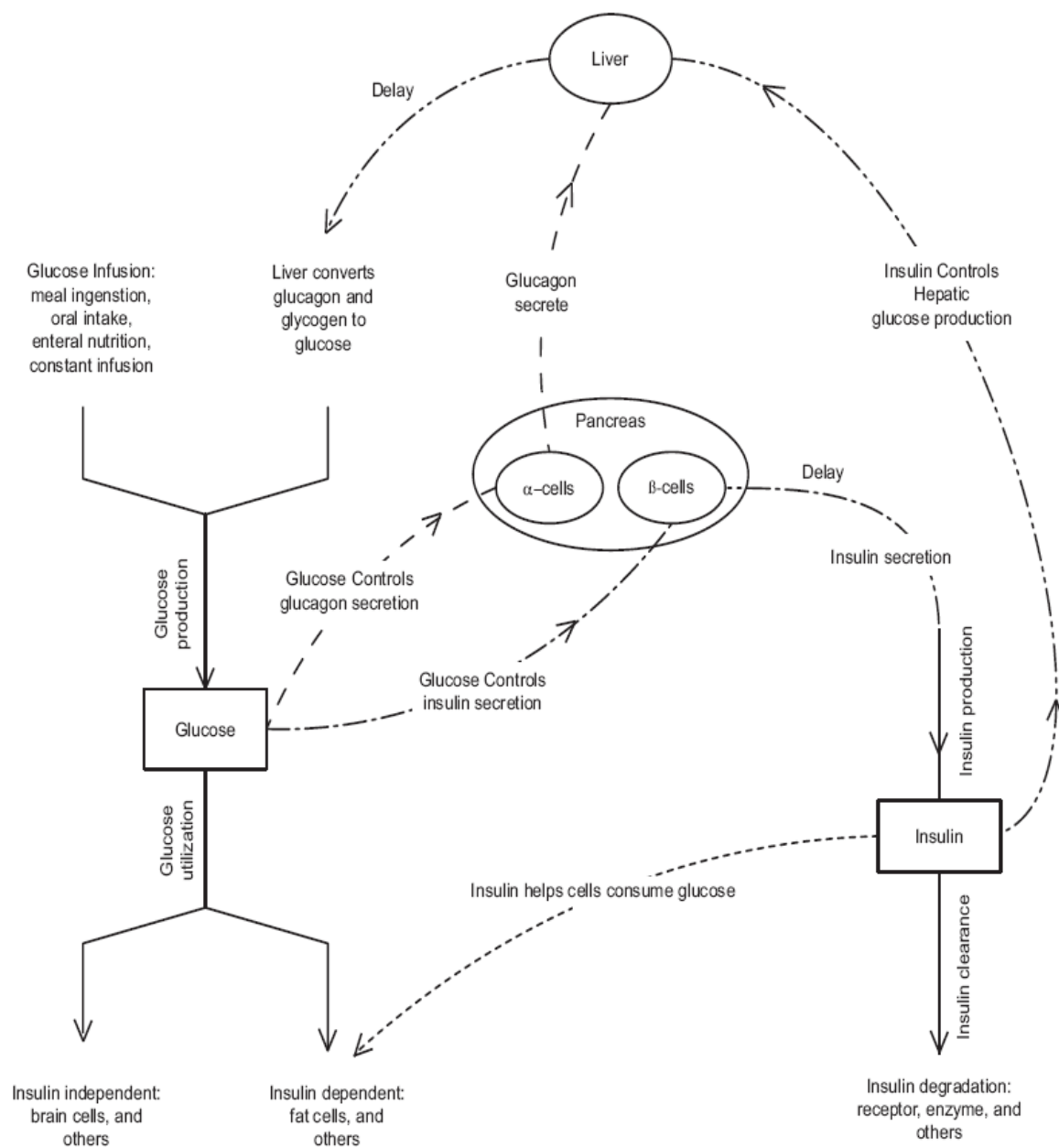


Figure 3.6: Two Time Delay Glucose-Insulin Regulatory Model. [50]

### 3.2. Linear Model:

The previous two time delay model is nonlinear. Therefore, we need to linearize the model to implement the proposed control strategies, so that it becomes easy to deal with and to analyze.

let  $G(t) = G_1(t) + G^*$  and  $I(t) = I_1(t) + I^*$  and using Taylor series expansion

$$G_1'(t) = G_{in} - f_2(G_1(t) + G^*) - f_3(G_1(t) + G^*)f_4(I_1(t) + I^*) + f_5(I_1(t - \tau_2) + I^*)$$

$$\begin{aligned} &= G_{in} - f_2(G^*) - G_1(t)f_2'(G^*) - f_3(G^*)f_4(I^*) - G_1(t)f_3'(G^*)f_4(I^*) - \\ &I_1(t)f_4'(I^*)f_3(G^*) + f_5(I^*) + I_1(t - \tau_2)f_5'(I^*) + HOT \end{aligned}$$

$$\begin{aligned} G_1'(t) &= (G_{in} - f_3(G^*)f_4(I^*) - f_5(I^*) - f_2(G^*)) - G_1(t)f_2'(G^*) \\ &- G_1(t)f_3'(G^*)f_4(I^*) - I_1(t)f_4'(I^*)f_3(G^*) + I_1(t - \tau_2)f_5'(I^*) + HOT \end{aligned}$$

$$I_1'(t) = f_1(G_1(t - \tau_1) + G^*) - d_i(I_1(t) + I^*)$$

$$= f_1(G^*) + f_1'(G^*)G_1(t - \tau_1) - d_i(I_1(t) + I^*) + HOT$$

So, after solving these two equations and ignoring the higher order term, the linear model will be as follows:

$$G_1'(t) = -[f_2'(G^*) + f_3'(G^*)f_4(I^*)]G_1(t) - f_3(G^*)f_4'(I^*)I_1(t) + f_5'(I^*)I_1(t - \tau_2)$$

$$I_1'(t) = f_1'(G^*)G_1(t - \tau_1) - d_i I_1(t) \tag{3.7}$$

So, we can write the system in the following form:

$$\begin{aligned}\frac{dG}{dt} &= -AG(t) - BI(t) - CI(t - \tau_2) \\ \frac{dI(t)}{dt} &= DG(t - \tau_1) - d_i I(t)\end{aligned}\tag{3.8}$$

where:

$$A = f_2'(G^*) + f_3'(G^*)f_4(I^*) > 0.$$

$$B = f_3(G^*)f_4'(I^*) > 0 .$$

$$C = -f_5'(I^*) > 0.$$

$$D = f_1'(G^*) > 0$$

The Standard Linear Time Delay System:

$$\dot{x}(t) = Ax(t) + A_{d1}x(t - \tau_1) + A_{d2}x(t - \tau_2) + Eu(t) + \Gamma w$$

$$y(t) = Cx(t) + Du(t)$$

where:

$$A = \begin{bmatrix} -A & -B \\ 0 & -C \end{bmatrix} ;$$

$$A_{d1} = \begin{bmatrix} 0 & 0 \\ D & 0 \end{bmatrix} ;$$

$$A_{d2} = \begin{bmatrix} 0 & -C \\ 0 & 0 \end{bmatrix};$$

Two methods are used to control the glucose- insulin regulatory system:

- 1) Controlling the system by using both insulin and glucose to keep the balance in the patient. However, this technique failed.
- 2) Controlling the system by using insulin dosage only while the glucose can be taken as carbohydrate by the patient. So, our goal is to deal only with hyperglycemia, in which the glucose level is above 140 mg/dl, and to reduce the glucose to Normoglycemia level (70-110 mg/dl). So, we have only one control input, and the input weight matrix will be as follows:

$$E = \begin{bmatrix} 0 \\ 1 \end{bmatrix};$$

So, if we linearized the model around the operating point (9500, 90), the system matrices:

$$A = \begin{bmatrix} -0.0902 & -0.6946 \\ 0 & -0.0600 \end{bmatrix}$$

$$A_{d1} = \begin{bmatrix} 0 & 0 \\ 0.0012 & 0 \end{bmatrix}$$

$$A_{d2} = \begin{bmatrix} 0 & -3.7594 \\ 0 & 0 \end{bmatrix}$$

## CHAPTER 4

### SOLUTION VIA LINEAR MATRIX INEQUALITY (LMI)

#### 4.1. Introduction

Linear Matrix Inequality (LMI) is a useful and powerful design tool in control engineering system identification areas because of the following factors:

1. A variety of design specifications and constraints can be expressed as LMIs.
2. Existence of efficient LMI solvers (using convex optimization algorithms).
3. Unlike the analytical techniques, multiple constraints or objectives can be often traced by using LMI techniques.

LMI techniques can be used also with a class of linear or nonlinear time delay systems for stability or control design. This chapter presents the LMI development for a linear system with two time delays (unknown constant – bounded type) based on  $H_\infty$  criteria for the following:

- (1) Stability analysis.
- (2) State feedback.



(3) Tracking.

## 4.2. Stability Analysis:

Consider the following plant with single time delay:

$$\begin{aligned}\dot{x}(t) &= Ax(t) + A_h x(t - \tau) + Bu(t) + \Gamma_o w(t) \\ y(t) &= Cx(t) + Du(t) + \psi_o w(t)\end{aligned}\tag{4.1}$$

$$z(t) = G_o x(t) + G_{do} x(t - \tau) + D_o u(t) + \Phi_o w(t).$$

where  $x(t) \in \mathbb{R}^n$  is the state vector,  $u(t) \in \mathbb{R}^m$  is the control input,  $w(t) \in \mathbb{R}^q$  is the disturbance input &  $z(t) \in \mathbb{R}^t$  is the controlled output and  $\tau$  is a constant time delay.

### Theorem:

The above plant will be stable if for  $0 < P = P^t$ ,  $0 < W = W^t$ ,  $0 < Q = Q^t$ , the following LMI is satisfied:

$$\mathcal{E} = \begin{bmatrix} E_{11} & E_{12} & \tau\theta & P\Gamma_o & G_o^t & -\tau A^t W \\ \bullet & E_{22} & -\tau Y & 0 & G_{do}^t & -\tau A_h^t W \\ \bullet & \bullet & -\tau W & 0 & 0 & 0 \\ \bullet & \bullet & \bullet & -\gamma^2 I & \Phi_o^t & -\tau \Gamma_o^t W \\ \bullet & \bullet & \bullet & \bullet & -I & 0 \\ \bullet & \bullet & \bullet & \bullet & \bullet & -\tau W \end{bmatrix} < 0 \tag{4.2}$$

where

$\theta \in \mathbb{R}^{n \times n}$ , and  $Y \in \mathbb{R}^{n \times n}$  are appropriate relaxation matrices.

$Q$  &  $W$  are weighting matrices.

$$E_{11} = PA + A^t P + \Theta + \Theta^t + Q$$

$$E_{12} = PA_h - \Theta + Y^t$$

$$E_{22} = -Y - Y^t - Q$$

**Proof:**

Consider the Lyapunov-Krasovskii Function:

$$V(t) = V_o(t) + V_a(t) + V_m(t) \quad (4.3)$$

$$V_o(t) = x^t(t)Px(t) \quad (4.4)$$

$$V_a(t) = \int_{-\tau}^0 \int_{t+s}^t \dot{x}^t(\alpha) W \dot{x}(\alpha) d\alpha ds \quad (4.5)$$

$$V_m(t) = \int_{t-\tau}^t x^t(s) Q x(s) ds \quad (4.6)$$

The first term is the standard to the delayless nominal system, and the second and the third terms correspond to the delay-dependent condition.

$$\dot{V}(t) = \dot{V}_o(t) + \dot{V}_a(t) + \dot{V}_m(t) \quad (4.7)$$

$$\dot{V}_o(t) = \dot{x}^t(t)Px(t) + x^t(t)P\dot{x}(t) = 2x^t(t)P\dot{x}(t)$$

$$\dot{V}_o(t) = 2x^t(t)P(Ax(t) + A_h x(t - \tau))$$

$$= 2x^t(t)P(Ax(t) + A_h x(t - \tau)) \quad (4.8)$$

$$\begin{aligned}
&= 2x^t(t)P[Ax(t) + A_h x(t - \tau)] + 2x^t(t)\theta \int_{t-\tau}^t \dot{x}(s) ds + 2x^t(t - \tau)Y \int_{t-\tau}^t \dot{x}(s) ds - \\
&\quad \left[ 2x^t(t) \theta \int_{t-\tau}^t \dot{x}(s) ds + 2x^t(t - \tau) Y \int_{t-\tau}^t \dot{x}(s) ds \right] \\
&= 2x^t(t)P[Ax(t) + A_h x(t - \tau)] + 2x^t(t)\theta[x(t) - x(t - \tau)] + 2x^t(t - \tau)Y[x(t) - \\
&\quad x(t - \tau)] - \left[ 2x^t(t) \theta \int_{t-\tau}^t \dot{x}(s) ds + 2x^t(t - \tau) Y \int_{t-\tau}^t \dot{x}(s) ds \right] \\
&= 2x^t(t)[PA + \theta]x(t) + 2x^t(t)[PA_h - \theta + Y^t]x(t - \tau) + 2x^t(t - \tau)(-Y)x(t - \tau) - \\
&\quad 2x^t(t) \theta \int_{t-\tau}^t \dot{x}(s) ds - 2x^t(t - \tau) Y \int_{t-\tau}^t \dot{x}(s) ds \\
&= x^t(t)PAx(t) + x^t(t)A^tPx(t) + x^t(t)\theta x(t) + x^t(t)\theta^t x(t) + 2x^t(t)[PA_h - \theta + \\
&\quad Y^t] x(t - \tau) + 2x^t(t - \tau) (-Y) x(t - \tau) - 2x^t(t) \theta \int_{t-\tau}^t \dot{x}(s) ds - 2x^t(t - \tau) \\
&\quad Y \int_{t-\tau}^t \dot{x}(s) ds \\
&\quad \frac{1}{\tau} \int_{t-\tau}^t [x^t(t)PA x(t) + x^t(t)A^tPx(t) + x^t(t)\theta x(t) + x^t(t)\theta^t x(t) + 2x^t(t)[PA_h - \theta + \\
&\quad Y^t] x(t - \tau) + 2x^t(t - \tau) (-Y) x(t - \tau) - 2x^t(t) \theta \tau \dot{x}(s) - 2x^t(t - \tau) Y \tau \dot{x}(s)] ds \\
&\quad (4.9)
\end{aligned}$$

Where,  $\theta \in \Re^{n \times n}$ , and  $Y \in \Re^{n \times n}$  are appropriate relaxation parameter matrices injected to facilitate the delay dependence analysis

$$V_a(t) = \int_{-\tau}^0 \int_{t+s}^t \dot{x}^t(\alpha) W \dot{x}(\alpha) d\alpha ds \quad (4.10)$$

The Lybanze Rule yields:

$$\dot{V}_a(t) = \int_{-\tau}^0 \frac{d}{dt} \left( \int_{t+s}^t \dot{x}^t(\alpha) W \dot{x}(\alpha) d\alpha \right) ds$$

$$\begin{aligned}
&= \int_{-\tau}^0 (0 + \dot{x}^t(t)W\dot{x}(t) - \dot{x}^t(t+s)W\dot{x}(t+s))ds \\
&= \int_{-\tau}^0 [\dot{x}^t(t)W\dot{x}(t) - (\dot{x}^t(t+s)W\dot{x}(t+s))]ds
\end{aligned}$$

$t + s = \alpha$  , then  $= d\alpha$  , when  $s = -\tau$  then  $\alpha = t - \tau$ , and when  $s = 0$  then  $\alpha = t$

thus:

$$= \int_{t-\tau}^t [(\dot{x}^t(t)W\dot{x}(t)) - (\dot{x}^t(s)W\dot{x}(s))] ds$$

For the third function:

$$\dot{V}_m(t) = \frac{1}{\tau} \int_{t-\tau}^t [x^t(t)Qx(t) - x^t(t-\tau)Qx(t-\tau)] ds \quad (4.10)$$

So, defining the state vector:

$$\chi(t, s) = [x^t(t) \quad x^t(t-\tau) \quad \dot{x}^t(s)]^t$$

$$\dot{V}(t) \leq (\chi^t(t, s)\Xi_h\chi(t, s) + (\dot{x}^t(t)W\dot{x}(t))) < 0$$

where

$$\Xi_h = \begin{bmatrix} PA + A^tP + \Theta + \Theta^t + Q & PA_h - \Theta + Y^t & \tau\Theta \\ \bullet & -Y - Y^t - Q & -\tau Y \\ \bullet & \bullet & -\tau W \end{bmatrix}$$

Next we use the term  $(\dot{x}^t(t)W\dot{x}(t))$  in

$$\dot{x}(t) = Ax(t) + A_hx(t-\tau)$$

Algebraic manipulation yields:

$$\tau \dot{x}^t(t) W \dot{x}(t) = \tau \chi^t \bar{A}^t W \bar{A} \chi$$

$$\dot{x}(t) = \begin{bmatrix} A & A_h & 0 \end{bmatrix} \begin{bmatrix} x(t) \\ x(t - \tau) \\ \dot{x}(s) \end{bmatrix}$$

$$= \bar{A} \chi(t, s) \triangleq \bar{A} \chi$$

Therefore:

$$\begin{aligned} \dot{V}(t) &= \chi^t \mathcal{E}_h \chi + \tau \chi^t \bar{A}^t W \bar{A} \chi \\ &= \chi^t [\mathcal{E}_h + \tau \bar{A}^t W \bar{A}] \chi \\ &= \chi^t [\mathcal{E}_h + \tau \bar{A}^t W W^{-1} W \bar{A}] \chi \\ &= \chi^t [\mathcal{E}_h + \tau \bar{A}^t W \tau^{-1} W^{-1} W \bar{A} \tau] \chi < 0 \end{aligned} \quad (4.12)$$

By using the Schur complement , if  $\mathcal{E} < 0$  then

$$\dot{V}(t) < 0 \quad \Rightarrow \quad \text{the system is internally stable.}$$

Considering the following performance measure:

$$J = \int_0^\infty (z^t(s) z(s) - \gamma^2 w^t(s) w(s)) ds \quad (4.13)$$

For any  $w(t) \in \mathcal{L}_2 [0, \infty) \neq 0$  and zero initial condition  $x(t) = 0$ , then we can rewrite the performance measure as follows:

$$\begin{aligned}
J &= \int_0^\infty \left( z^t(s)z(s) - \gamma^2 w^t(s)w(s) + \dot{V}(s) - \dot{V}(s) \right) ds \\
&\leq \int_0^\infty \left( z^t(s)z(s) - \gamma^2 w^t(s)w(s) + \dot{V}(s) \right) ds
\end{aligned}$$

Let  $\bar{\chi}(t, s) = [x^t(t) \quad x^t(t - \tau) \quad \dot{x}^t(s) \quad w^t(t)]^t$

Then, following the same development as before, and by using the Schur complement, it is clear that

$$z^t(s)z(s) - \gamma^2 w^t(s)w(s) + \dot{V}(x) = \bar{\chi}^t(t, s) \bar{E} \bar{\chi}(t, s) < 0$$

for any arbitrary  $s \in [t, \infty)$ , which implies for any  $w(t) \in \mathcal{L}_2 [0, \infty) \neq 0$  that  $J < 0$  leading to  $\|z(t)\|_2 < \gamma \|w(t)\|_2$

By using the Schur complement, and by including the performance measure  $J$ , the LMI (4.2) will be obtained.

### 4.3. State Feedback Derivation:

Applying the state-feedback control  $u(t) = Kx(t)$   $A_c = A + BK$ . It then follows from the previous analysis that the resulting closed-loop system is delay-independent and asymptotically stable with  $\mathcal{L}_2$  performance bound if there exist weighting matrices  $M$ ;  $Q$ ; and parameter matrices  $\Theta$ ;  $\Upsilon$  and scalar  $\gamma > 0$  satisfying the following LMI:

$$E_{c3} = \begin{bmatrix} E_{c311} & E_{c312} & \tau\theta_1 & M\Gamma_o & MG_o^t & -\tau MA^t \\ \bullet & E_{c322} & -\tau Y_1 & 0 & MG_{do}^t & -\tau MA_h^t \\ \bullet & \bullet & -\tau \varepsilon M & 0 & 0 & 0 \\ \bullet & \bullet & \bullet & -\gamma^2 I & \Phi_o^t & -\tau \Gamma_o^t \\ \bullet & \bullet & \bullet & \bullet & -I & 0 \\ \bullet & \bullet & \bullet & \bullet & \bullet & -\tau \varepsilon^{-1} M \end{bmatrix} < 0 \quad (4.14)$$

where:

$$\begin{aligned} E_{c311} &= A_c M + M A_c^t + \theta_1 + \theta_1^t + Q_1 \\ &= AM + B\mathcal{Y} + MA^t + \mathcal{Y}^t B^t + \theta_1 + \theta_1^t + Q_1 \end{aligned}$$

$$E_{c312} = A_{do} M - \theta_1 + Y_1^t$$

$$E_{c322} = -Y_1 - Y_1^t - Q_1$$

### Proof:

From LMI (4.2) and replacing A by Ac=A+BK, the following LMI is obtained:

$$E_C = \begin{bmatrix} E_{c11} & E_{c12} & \tau\theta & P\Gamma_o & G_o^t & -\tau A^t W \\ \bullet & E_{c22} & -\tau Y & 0 & G_{do}^t & -\tau A_h^t W \\ \bullet & \bullet & -\tau W & 0 & 0 & 0 \\ \bullet & \bullet & \bullet & -\gamma^2 I & \Phi_o^t & -\tau \Gamma_o^t W \\ \bullet & \bullet & \bullet & \bullet & -I & 0 \\ \bullet & \bullet & \bullet & \bullet & \bullet & -\tau W \end{bmatrix} < 0$$

where

$$E_{c11} = PA_c + A_c^t P + \theta + \theta^t + Q$$

$$E_{c12} = E_{12} = PA_{do} - \theta + Y^t$$

$$E_{c22} = E_{22} = -Y - Y^t - Q$$

So, to develop the closed loop LMI , we do the following steps:

1 We have to rewrite the LMI  $\mathcal{E}$  so that:

$$\mathcal{E}_{C1} = [I \ I \ I \ I \ I \ W^{-1}] \mathcal{E}_C [I \ I \ I \ I \ I \ W^{-1}]^t$$

$$\mathcal{E}_{C1} = \begin{bmatrix} \mathcal{E}_{c11} & \mathcal{E}_{c12} & \tau\theta & P\Gamma_o & G_o^t & -\tau A^t \\ \bullet & \mathcal{E}_{c22} & -\tau Y & 0 & G_{do}^t & -\tau A_h^t \\ \bullet & \bullet & -\tau W & 0 & 0 & 0 \\ \bullet & \bullet & \bullet & -\gamma^2 I & \Phi_o^t & -\tau \Gamma_o^t \\ \bullet & \bullet & \bullet & \bullet & -I & 0 \\ \bullet & \bullet & \bullet & \bullet & \bullet & -\tau W^{-1} \end{bmatrix} < 0 \quad (4.14)$$

2 Multiply the new LMI  $\mathcal{E}_1$  by the following terms:

$$\mathcal{E}_{C2} = [M \ M \ M \ I \ I \ I] \mathcal{E}_{C1} [M \ M \ M \ I \ I \ I]^t$$

and substitute  $P = M^{-1}$

$$\mathcal{E}_{c2} = \begin{bmatrix} M\mathcal{E}_{c11}M & M\mathcal{E}_{c12}M & \tau M\theta M & M\Gamma_o & MG_o^t & -\tau MA^t \\ \bullet & M\mathcal{E}_{c22}M & -\tau MYM & 0 & MG_{do}^t & -\tau MA_h^t \\ \bullet & \bullet & -\tau MWM & 0 & 0 & 0 \\ \bullet & \bullet & \bullet & -\gamma^2 I & \Phi_o^t & -\tau \Gamma_o^t \\ \bullet & \bullet & \bullet & \bullet & -I & 0 \\ \bullet & \bullet & \bullet & \bullet & \bullet & -\tau W^{-1} \end{bmatrix} < 0 \quad (4.15)$$

3 Set  $W = \varepsilon M^{-1}$ , then  $W^{-1} = \varepsilon^{-1} M$  and the LMI can be written as follows:

$$\mathcal{E}_{c3} = \begin{bmatrix} M\mathcal{E}_{c11}M & M\mathcal{E}_{c12}M & \tau M\theta M & M\Gamma_o & MG_o^t & -\tau MA^t \\ \bullet & M\mathcal{E}_{c22}M & -\tau MYM & 0 & MG_{do}^t & -\tau MA_h^t \\ \bullet & \bullet & -\tau \varepsilon M & 0 & 0 & 0 \\ \bullet & \bullet & \bullet & -\gamma^2 I & \Phi_o^t & -\tau \Gamma_o^t \\ \bullet & \bullet & \bullet & \bullet & -I & 0 \\ \bullet & \bullet & \bullet & \bullet & \bullet & -\tau \varepsilon^{-1} M \end{bmatrix} < 0 \quad (4.16)$$



Now, we need to simplify the LMI and make all its terms linear , we do the following:

$$\mathcal{E}_{c311} = M\mathcal{E}_{c11}M = M[PA_c + A_c^t P^t + \theta_c + \theta_c^t + Q]M$$

$$= A_c M + M A_c^t + M \theta_c M + M \theta_c^t M + M Q M$$

$$\mathcal{E}_{c312} = M\mathcal{E}_{c12}M = M[PA_{do} - \theta + \gamma^t]M = A_{do} M - M \theta_c M + M \gamma_c^t M$$

$$\mathcal{E}_{c313} = M\mathcal{E}_{c22}M = M[-\gamma_c - \gamma_c^t - Q]M = -M \gamma_c M - M \gamma_c^t M - M Q M$$

However,

$$A_c = A + BK \text{ and } G_s = G_o + DK$$

$$\text{Let } \mathcal{Y} = KM$$

$$\text{Then } A_c M = AM + BKM = AM + B\mathcal{Y}$$

$$G_s M = G_o M + DKM = G_o M + D\mathcal{Y}$$

$$\text{However } D=0, \text{ So, } G_s = G_o$$

Let

$$\theta_1 = M \theta_c M$$

$$Q_1 = M Q M$$

$$\gamma_1 = M \gamma_c M$$

By using the performance Measure J , the LMI (4.14) is obtained.

#### 4.4. Extension to Two Time Delay System

$$\dot{x}(t) = Ax(t) + A_{h1}x(t - \tau_1) + A_{h1}x(t - \tau_2) + Bu(t) + \Gamma_o w(t) \quad (4.17)$$

$$y(t) = Cx(t) + Du(t) + \psi_o w(t)$$

$$z(t) = G_o x(t) + G_{do1}x(t - \tau_1) + G_{do2}x(t - \tau_2) + D_o u(t) + \Phi_o w(t)$$

The above plant will be stable if for  $0 < P = P^t$ ,  $0 < W_1 = W_1^t$ ,  $0 < W_2 = W_2^t$ ,  $0 < Q_1 = Q_1^t$ ,  $0 < Q_2 = Q_2^t$ ,  $\Theta_1 \in \Re^{n \times n}$ ,  $\Theta_2 \in \Re^{n \times n}$  and  $\Upsilon_1 \in \Re^{n \times n}$ ,  $\Upsilon_2 \in \Re^{n \times n}$  the following LMI is satisfied:

$$\begin{bmatrix} \mathcal{E}_{111} & \mathcal{E}_{121} & \mathcal{E}_{122} & \tau_1 \Theta_1 & \tau_2 \Theta_2 & P\Gamma_o & G_o^t & -\tau_1 A^t W_1 & -\tau_2 A^t W_2 \\ \bullet & \mathcal{E}_{222} & 0 & -\tau_1 \Upsilon_1 & 0 & 0 & G_{do1}^t & -\tau_1 A_{h1}^t W_1 & -\tau_2 A_{h1}^t W_2 \\ \bullet & \bullet & \mathcal{E}_{333} & 0 & -\tau_2 \Upsilon_2 & 0 & G_{do2}^t & -\tau_1 A_{h2}^t W_1 & -\tau_2 A_{h2}^t W_2 \\ \bullet & \bullet & \bullet & -\tau_1 W_1 & 0 & 0 & 0 & 0 & 0 \\ \bullet & \bullet & \bullet & \bullet & -\tau_2 W_2 & 0 & 0 & 0 & 0 \\ \bullet & \bullet & \bullet & \bullet & \bullet & -\gamma^2 I & \Phi_o^t & -\tau_1 \Gamma_o^t W_1 & -\tau_2 \Gamma_o^t W_2 \\ \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & -I & 0 & 0 \\ \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & -\tau_1 W_1 & 0 \\ \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & -\tau_2 W_2 \end{bmatrix} < 0$$

(4.18)

where:

$$\mathcal{E}_{111} = PA + A^t P + \Theta_1 + \Theta_1^t + \Theta_2 + \Theta_2^t + Q_1 + Q_2$$

$$\mathcal{E}_{121} = PA_{h1} - \Theta_1 + \Upsilon_1^t$$

$$\mathcal{E}_{122} = PA_{h2} - \Theta_2 + \Upsilon_2^t$$

$$\mathcal{E}_{222} = -Y_1 - Y_1^t - Q_1$$

$$\mathcal{E}_{333} = -Y_2 - Y_2^t - Q_2$$

**Proof:**

Consider the following Lyapunov-Krasovskii functions:

$$V_2(t) = V_{o2}(t) + V_{a2}(t) + V_{m2}(t)$$

$$V_{o2}(t) = x^t(t)Px(t)$$

$$V_{a2}(t) = \int_{-\tau_1}^0 \int_{t+s}^t \dot{x}^t(\alpha)W_1\dot{x}(\alpha)d\alpha ds + \int_{-\tau_2}^0 \int_{t+s}^t \dot{x}^t(\alpha)W_2\dot{x}(\alpha)d\alpha ds$$

(4.19)

$$V_{m2}(t) = \int_{t+\tau_1}^t x^t(s)Q_1x(s)ds + \int_{t+\tau_2}^t x^t(s)Q_2x(s)ds$$

(4.20)

$$= \int_{t-\tau_1}^t x^t(s)Q_1x(s)ds + \int_{t-\tau_2}^t x^t(s)Q_2x(s)ds$$

(4.21)

Following the procedure done in the previous sections, we can extend the LMI for two time delay, as follows:

$$\begin{aligned} V_{o2}(t) = & \frac{1}{\tau_1} \int_{t-\tau_1}^t \left[ x^t(t)PAx(t) + x^t(t)A^tPx(t) + x^t(t)\Theta_1x(t) + x^t(t)\Theta_1^t x(t) + \right. \\ & 2x^t(t)[PA_{do1} - \Theta_1 + Y_1^t] x(t - \tau_1) + 2x^t(t - \tau_1)(-Y_1)x(t - \tau_1) - 2x^t(t)\Theta_1\tau_1\dot{x}(s) - \\ & \left. 2x^t(t - \tau_1)Y_1\tau_1\dot{x}(s) \right] ds + \end{aligned}$$

$$\begin{aligned}
& \frac{1}{\tau_2} \int_{t-\tau_2}^t [x^t(t)PA x(t) + x^t(t) A^t P x(t) + x^t(t) \Theta_2 x(t) + x^t(t) \Theta_2^t x(t) + \\
& 2x^t(t)[PA_{d\circ 2} - \Theta_1 + Y_2^t] x(t - \tau_2) + 2x^t(t - \tau_2)(-Y_2) x(t - \tau_2) - \\
& 2x^t(t) \Theta_2 \tau_2 \dot{x}(s) - 2x^t(t - \tau_2) Y_2 \tau_2 \dot{x}(s)] ds \quad (4.22)
\end{aligned}$$

$$\begin{aligned}
V_{a2}(t) = & \int_{t-\tau_1}^t [(\dot{x}^t(t)W_1\dot{x}(t)) - (\dot{x}^t(s)W_1\dot{x}(s))] ds + \int_{t-\tau_2}^t [(\dot{x}^t(t)W_2\dot{x}(t)) - \\
& (\dot{x}^t(s)W_2\dot{x}(s))] ds \quad (4.23)
\end{aligned}$$

$$\begin{aligned}
V_{m2}(t) = & \frac{1}{\tau_1} \int_{t-\tau_1}^t [x^t(t)Q_1x(t) - x^t(t - \tau_1)Q_1x(t - \tau_1)] ds + \frac{1}{\tau_2} \int_{t-\tau_2}^t [x^t(t)Q_2x(t) - \\
& x^t(t - \tau_2) Q_2 x(t - \tau_2)] ds \quad (4.24)
\end{aligned}$$

since

$$\dot{x}(t) = Ax(t) + A_{h1}x(t - \tau_1) + A_{h2}x(t - \tau_2)$$

Next we use the terms  $(\dot{x}^t(t)W_1\dot{x}(t)) - (\dot{x}^t(s)W_1\dot{x}(s))$

Algebraic manipulation yields:

$$\begin{aligned}
\dot{x}^t(t)[\tau_1 W_1 + \tau_2 W_2]\dot{x}(t) &= \chi^t \bar{A}^t [\tau_1 W_1 + \tau_2 W_2] \bar{A} \chi \\
&= [A \quad A_{h1} \quad A_{h2} \quad 0] \begin{bmatrix} x(t) \\ x(t - \tau_1) \\ x(t - \tau_2) \\ \dot{x}(s) \end{bmatrix} \\
&= \bar{A} \chi(t, s) \triangleq \bar{A} \chi
\end{aligned}$$

Therefore:

$$\begin{aligned}
\dot{V}(t) &= \chi^t \mathcal{E}_h \chi + \chi^t \bar{A}^t [\tau_1 W_1 + \tau_2 W_2] \bar{A} \chi \\
&= \chi^t [\mathcal{E}_h + \tau \bar{A}^t [\tau_1 W_1 + \tau_2 W_2] \bar{A}] \chi
\end{aligned} \tag{4.25}$$

By using the Schur complement and the same performance measure we will obtain with the LMI (4.18)

#### 4.5. State Feedback for Two time delay Case

The plant with two time delays (4.17) is stable if for  $0 < P = P^t$ ,  $0 < Q_{11} = Q_{11}^t$ ,  $0 < Q_{21} = Q_{21}^t$ ,  $\theta_{11} \in \mathbb{R}^{n \times n}$ ,  $\theta_{21} \in \mathbb{R}^{n \times n}$  and  $Y_{11} \in \mathbb{R}^{n \times n}$ ,  $Y_{21} \in \mathbb{R}^{n \times n}$  the following LMI is satisfied:

$$\begin{bmatrix}
\mathcal{E}_{11a} & \mathcal{E}_{121a} & \mathcal{E}_{122a} & \tau_1 \theta_{11} & \tau_2 \theta_{12} & M \Gamma_o & M G_0^t & -\tau_1 M A^t & -\tau_2 M A^t \\
\bullet & \mathcal{E}_{221a} & 0 & -\tau_1 Y_{11} & 0 & 0 & M G_{do1}^t & -\tau_1 M A_{h1}^t & -\tau_2 M A_{h1}^t \\
\bullet & \bullet & \mathcal{E}_{332a} & 0 & -\tau_2 Y_{21} & 0 & M G_{do2}^t & -\tau_1 M A_{h2}^t & -\tau_2 M A_{h2}^t \\
\bullet & \bullet & \bullet & -\tau_1 \varepsilon_1^{-1} M & 0 & 0 & 0 & 0 & 0 \\
\bullet & \bullet & \bullet & \bullet & -\tau_2 \varepsilon_2^{-1} M & 0 & 0 & 0 & 0 \\
\bullet & \bullet & \bullet & \bullet & \bullet & -\gamma^2 I & \hat{\Phi}_o^t & -\tau_1 \hat{\Gamma}_o^t & -\tau_2 \Gamma_o^t \\
\bullet & \bullet & \bullet & \bullet & \bullet & \bullet & -I & 0 & 0 \\
\bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & -\tau_1 \varepsilon_1^{-1} M & 0 \\
\bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & -\tau_2 \varepsilon_2^{-1} M
\end{bmatrix} < 0 \tag{4.26}$$

where:

$$\begin{aligned}
\mathcal{E}_{11a} &= A_c M + M A_c^t + \theta_{11} + \theta_{11}^t + \theta_{21} + \theta_{21}^t + Q_{11} + Q_{21} \\
&= A M + B Y + M A^t + Y^t B^t + \theta_{11} + \theta_{11}^t + \theta_{21} + \theta_{21}^t + Q_{11} + Q_{21}
\end{aligned}$$

$$Y = K M$$

$$\mathcal{E}_{121a} = A_{do1} M - \theta_{11} + Y_{11}^t$$

$$\mathcal{E}_{122a} = A_{do2}M - \Theta_{11} + Y_{21}^t$$

$$\mathcal{E}_{c322} = -Y_{11} - Y_{11}^t - Q_{11}$$

$$\mathcal{E}_{c322} = -Y_{21} - Y_{21}^t - Q_{21}$$

To prove this LMI, we apply the same procedure as for one time delay to LMI (4.26).

#### 4.6. Tracking:

In the previous sections, we develop the LMI by using it to stabilize the plant. However, we need also, in addition to stabilizing the plant, to control its behavior in the transient zone, so that it can follow the desired behavior. This is done by choosing a model which has the desired characteristics which the plant should track by forcing the error between model and plant to be minimum. The LMI technique is used to do that because we can augment the plant and the model in one LMI and we can do the stabilizing and the tracking also in the same LMI.

So, if we consider the plant and model as follows:

$$\dot{x}(t) = Ax(t) + A_h x(t - \tau) + Bu(t) + \Gamma_o w(t) \quad (4.27)$$

$$\dot{x}_m(t) = A_m x_m(t) + A_{hm} x_m(t - \tau)$$

$$\text{where } u(t) = Ke(t) = K(x_m(t) - x(t)) \quad (4.28)$$

$$\dot{e}(t) = A_m(x_m(t) - x(t)) + (A_m - A)x(t) - BKe(t) + A_{hm}(x_m(t - \tau) - x(t - \tau))$$

$$+(A_{hm} - A_h)x(t - \tau)$$

$$\dot{e}(t) = (A_m - BK)e(t) + (A_m - A)x(t) + A_{hm}e(t - \tau) + (A_{hm} - A_h)x(t - \tau)$$

$$\dot{x}(t) = Ax(t) + A_hx(t - \tau) + BKe(t) \quad (4.29)$$

$$\hat{X} = \begin{bmatrix} \dot{x}(t) \\ e(t) \end{bmatrix} = \begin{bmatrix} A & BK \\ A_m - A & A_m - BK \end{bmatrix} \begin{bmatrix} x(t) \\ e(t) \end{bmatrix} + \begin{bmatrix} A_h & 0 \\ A_{hm} - A_h & A_{hm} \end{bmatrix} \begin{bmatrix} x(t - \tau) \\ e(t - \tau) \end{bmatrix} + \Gamma_o w(t) \quad (4.30)$$

$$\hat{\dot{X}}(t) = \hat{A}\hat{X}(t) + \hat{A}_h\hat{X}(t - \tau) + \Gamma_o w(t)$$

So, the plant will track the model if  $0 < \hat{P} = \hat{P}^t, 0 < \hat{Q} = \hat{Q}^t, 0 < \hat{W} = \hat{W}^t$  &  $\hat{\Theta} \in$

$\Re^{n \times n}, \hat{Y} \in \Re^{n \times n}$ . The new LMI is satisfied:

$$\mathcal{E} = \begin{bmatrix} \mathcal{E}_{11} & \mathcal{E}_{12} & \tau \hat{\Theta} & \hat{P} \Gamma_o & \hat{G}_o^t & -\tau \hat{A}^t \hat{W} \\ \bullet & \mathcal{E}_{22} & -\tau \hat{Y} & 0 & \hat{G}_{do}^t & -\tau \hat{A}_h^t \hat{W} \\ \bullet & \bullet & -\tau \hat{W} & 0 & 0 & 0 \\ \bullet & \bullet & \bullet & -\gamma^2 I & \Phi_o^t & -\tau \Gamma_o^t \hat{W} \\ \bullet & \bullet & \bullet & \bullet & -I & 0 \\ \bullet & \bullet & \bullet & \bullet & \bullet & -\tau \hat{W} \end{bmatrix} < 0 \quad (4.31)$$

where

$$\mathcal{E}_{11} = \hat{P}\hat{A} + \hat{A}^t\hat{P} + \hat{\Theta} + \hat{\Theta}^t + \hat{Q}$$

$$\mathcal{E}_{12} = \hat{P}\hat{A}_h - \hat{\Theta} + \hat{Y}^t$$

$$\mathcal{E}_{22} = -\hat{Y} - \hat{Y}^t - \hat{Q}$$

$$\hat{G}_o = [G_o \ 0]^t$$

$$\hat{G}_{do} = [G_{do} \quad 0]^t$$

**Proof:**

Using the same stability analysis as before

$$\dot{V}_{2r}(t) = \dot{V}_{o2r}(t) + \dot{V}_{a2r}(t) + \dot{V}_{m2r}(t) \quad (4.32)$$

where :

$$V_{o2r}(t) = \hat{X}^t(t) \hat{P} \hat{X}(t) \quad (4.33)$$

$$V_{a2r}(t) = \int_{-\tau}^0 \int_{t+s}^t \hat{X}^t(\alpha) \hat{W} \hat{X}(\alpha) d\alpha ds \quad (4.34)$$

$$V_{m2r}(t) = \int_{t+\tau(t)}^t \hat{X}^t(t) \hat{Q} \hat{X}(t) ds = \int_{t-\tau}^t \hat{X}^t(t) \hat{Q} \hat{X}(t) ds \quad (4.35)$$

$$\begin{aligned} \dot{V}_{o2r}(t) &= \dot{\hat{X}}^t(t) \hat{P} \hat{X}(t) + \hat{X}^t(t) \hat{P} \dot{\hat{X}}(t) = 2\hat{X}^t(t) \hat{P} \dot{\hat{X}}(t) \\ &= 2\hat{X}^t(t) \hat{P} [\hat{A} \hat{X}(t) + \hat{A}_{h1} \hat{X}(t - \tau_1) + \Gamma_o w(t)] \end{aligned} \quad (4.36)$$

$$\dot{V}_{a2r}(t) = \int_{-\tau}^0 [\hat{X}^t(t) \hat{W} \dot{\hat{X}}(t) - \hat{X}^t(t+s) \hat{W} \dot{\hat{X}}(t+s)] ds$$

$$\dot{V}_{a2r}(t) = \int_{t-\tau}^t [\dot{\hat{X}}^t(t) \hat{W} \hat{X}(t) - \dot{\hat{X}}^t(s) \hat{W} \hat{X}(s)] ds \quad (4.37)$$

$$\begin{aligned} \dot{V}_{m2r}(t) &= \hat{X}^t(t) \hat{Q} \dot{\hat{X}}(t) - \hat{X}^t(t-\tau) \hat{Q} \dot{\hat{X}}(t-\tau) \\ &= \frac{1}{\tau} \int_{t-\tau}^t [\hat{X}^t(t) \hat{Q} \hat{X}(t) - \hat{X}^t(t-\tau) \hat{Q} \hat{X}(t-\tau)] ds \end{aligned} \quad (4.38)$$

Again, consider the NLDT System with  $u(.) \equiv 0$ , and let



$$\chi_r(t, s) = \begin{bmatrix} \hat{X}^t(t) & \hat{X}(t - \tau) & \hat{X}(s) \end{bmatrix}^t$$

$$\dot{V}_{2r}(t) \leq (\chi_r^t(t, s) \mathcal{E}_{h2} \chi_r(t, s) + \hat{X}^t(t) \hat{W} \hat{X}(t)) < 0 \quad (4.39)$$

where

$$\mathcal{E}_h = \begin{bmatrix} \hat{P}\hat{A} + \hat{A}^t\hat{P} + \hat{\Theta} + \hat{\Theta}^t + \hat{Q} & \hat{P}\hat{A}_h - \hat{\Theta} + \hat{Y}^t & \tau\hat{\Theta} \\ \bullet & -\hat{Y} - \hat{Y}^t - \hat{Q} & -\tau\hat{Y} \\ \bullet & \bullet & -\tau\hat{W} \end{bmatrix}$$

Doing the same mathematical manipulation:

$$\tau \hat{X}^t(t) \hat{W} \hat{X}(t) = \tau \chi_r^t \tilde{A}^t \tilde{W} \tilde{A} \chi_r$$

$$\hat{X}(t) = \begin{bmatrix} \hat{A} & \hat{A}_h & 0 \end{bmatrix} \begin{bmatrix} \hat{X}(t) \\ \hat{X}(t - \tau) \\ \hat{X}(s) \end{bmatrix}$$

$$= \tilde{A} \chi_r(t, s) \triangleq \tilde{A} \chi_r$$

Therefore:

$$\dot{V}(t) = \chi_r^t \mathcal{E}_h \chi_r + \tau \chi_r^t \tilde{A}^t \tilde{W} \tilde{A} \chi_r$$

$$= \chi_r^t [\mathcal{E}_h + \tau \tilde{A}^t \tilde{W} \tilde{A}] \chi_r$$

$$= \chi_r^t [\mathcal{E}_h + \tau \tilde{A}^t \tilde{W} \tilde{W}^{-1} \tilde{W} \tilde{A}] \chi_r$$

$$= \chi_r^t [\mathcal{E}_h + \tau \tilde{A}^t \tilde{W} \tau^{-1} \tilde{W}^{-1} \tilde{W} \tilde{A} \tau] \chi_r < 0 \quad (4.40)$$

or

$$\dot{V}(t) < \chi_r^t \mathcal{E} \chi_r < 0$$

By using the Schur complement and the same performance measure

$$J = \int_0^\infty \left( z^t(s)z(s) - \gamma^2 w^t(s)w(s) + \dot{V}(s) - \dot{V}(s) \right) ds$$

the LMI (4.31) is obtained.

### Closed Loop:

Applying the same procedure as in the state feedback section, the augmented plant is

stable and tracks the model for  $0 < \hat{P} = \hat{P}^t, 0 < \hat{Q}_1 = \hat{Q}_1^t, 0 < \hat{Q}_2 = \hat{Q}_2^t, 0 < \hat{W}_i = \hat{W}_i^t, \hat{\Theta} \in \mathfrak{R}^{n \times n}, \hat{Y} \in \mathfrak{R}^{n \times n}$

The new LMI is satisfied:

$$\begin{bmatrix} \mathcal{E}_{11a} & \mathcal{E}_{121a} & \tau_1 \Theta_1 & \hat{M} \hat{F}_o & \hat{M} \hat{G}_o^t & -\tau_1 \hat{M} A^t \\ \bullet & \mathcal{E}_{22a} & -\tau_1 \hat{Y} & 0 & \hat{M} \hat{G}_{do1}^t & -\tau_1 \hat{M} A_{h1}^t \\ \bullet & \bullet & -\tau_1 \hat{W}_{i1} & 0 & 0 & 0 \\ \bullet & \bullet & \bullet & -\gamma^2 I & \hat{\Phi}_o^t & -\tau_1 \hat{F}_o^t \\ \bullet & \bullet & \bullet & \bullet & -I & 0 \\ \bullet & \bullet & \bullet & \bullet & \bullet & -\tau_1 \hat{W}_i \end{bmatrix} < 0 \quad (4.41)$$

where:

$$\mathcal{E}_{11a} = \hat{M} \hat{A} + \hat{A}^t \hat{M} - \hat{B} \hat{Y} - \hat{Y}^t \hat{B}^t + \hat{\Theta} + \hat{\Theta}^t + \hat{Q}$$

$$\hat{Y} = K \hat{M}$$

$$\mathcal{E}_{12a} = \mathcal{E}_{12} = \hat{M}\hat{A}_h - \hat{\Theta} + \hat{Y}^t$$

$$\mathcal{E}_{22a} = -\hat{Y} - \hat{Y}^t - \hat{Q}$$

$$\hat{G}_o = [G_o \quad 0]^t$$

$$\hat{G}_{do} = [G_{do} \quad 0]^t$$

$$\hat{W}_i = \hat{W}^{-1}$$

#### 4.6. Tracking Development for Two Time Delay

Tracking derivation for the two time delay case can be obtained by following the same procedure as for one time delay. So, we consider the plant and model as follows:

$$\dot{x}(t) = Ax(t) + A_{h1}x(t - \tau_1) + A_{h2}x(t - \tau_2) + Bu(t) + \Gamma_o w(t)$$

$$\dot{x}_m(t) = A_m x_m(t) + A_{hm_1}x_m(t - \tau_1) + A_{hm_2}x_m(t - \tau_2)$$

where  $u(t) = Ke(t) = K(x_m(t) - x(t))$

$$\begin{aligned} \hat{X} = \begin{bmatrix} \dot{x}(t) \\ e(t) \end{bmatrix} &= \begin{bmatrix} A & BK \\ A_m - A & A_m - BK \end{bmatrix} \begin{bmatrix} x(t) \\ e(t) \end{bmatrix} + \begin{bmatrix} A_{h1} & 0 \\ A_{hm_1} - A_{h1} & A_{hm_1} \end{bmatrix} \begin{bmatrix} x(t - \tau_1) \\ e(t - \tau_1) \end{bmatrix} + \\ &\begin{bmatrix} A_{h2} & 0 \\ A_{hm_2} - A_{h2} & A_{hm_2} \end{bmatrix} \begin{bmatrix} x(t - \tau_2) \\ e(t - \tau_2) \end{bmatrix} + \Gamma_o w(t) \end{aligned} \quad (4.42)$$

$$\hat{X}(t) = \hat{A}\hat{X}(t) + \hat{A}_{h1}\hat{X}(t - \tau_1) + \hat{A}_{h2}\hat{X}(t - \tau_2) + \Gamma_o w(t)$$

After this analysis , we can formulate the LMI for open loop case and the closed loop as follows:

(1) Open Loop:

the plant will track the model for  $0 < \hat{P} = \hat{P}^t, 0 < \hat{Q}_1 = \hat{Q}_1^t, 0 < \hat{Q}_2 = \hat{Q}_2^t, 0 < \hat{W}_1 = \hat{W}_1^t, 0 < \hat{W}_2 = \hat{W}_2^t$ ,  $\hat{\Theta}_1 \in \mathbb{R}^{n \times n}, \hat{\Theta}_2 \in \mathbb{R}^{n \times n}, \hat{Y}_1 \in \mathbb{R}^{n \times n}, \hat{Y}_2 \in \mathbb{R}^{n \times n}$  and the new LMI is satisfied:

$$\begin{bmatrix} \mathcal{E}_{111} & \mathcal{E}_{121} & \mathcal{E}_{122} & \tau_1 \hat{\Theta}_1 & \tau_2 \hat{\Theta}_2 & \hat{P} \hat{\Gamma}_o & \hat{G}_o^t & -\tau_1 A^t \hat{W}_1 & -\tau_2 A^t \hat{W}_2 \\ \bullet & \mathcal{E}_{221} & 0 & -\tau_1 \hat{Y}_1 & 0 & 0 & \hat{G}_{do1}^t & -\tau_1 A_{h1}^t \hat{W}_1 & -\tau_2 A_{h1}^t \hat{W}_2 \\ \bullet & \bullet & \mathcal{E}_{332} & 0 & -\tau_2 \hat{Y}_2 & 0 & \hat{G}_{do2}^t & -\tau_1 A_{h2}^t \hat{W}_1 & -\tau_2 A_{h2}^t \hat{W}_2 \\ \bullet & \bullet & \bullet & -\tau_1 \hat{W}_1 & 0 & 0 & 0 & 0 & 0 \\ \bullet & \bullet & \bullet & \bullet & -\tau_2 \hat{W}_2 & 0 & 0 & 0 & 0 \\ \bullet & \bullet & \bullet & \bullet & \bullet & -\gamma^2 I & \hat{\Phi}_o^t & -\tau_1 \Gamma_o^t \hat{W}_1 & -\tau_2 \Gamma_o^t \hat{W}_2 \\ \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & -I & 0 & 0 \\ \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & -\tau_1 \hat{W}_1 & 0 \\ \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & -\tau_2 \hat{W}_2 \end{bmatrix} < 0$$

(4.44)

where:

$$\mathcal{E}_{111} = \hat{P} \hat{A} + \hat{A}^t \hat{P} + \hat{\Theta}_1 + \hat{\Theta}_1^t + \hat{\Theta}_2 + \hat{\Theta}_2^t + \hat{Q}_1 + \hat{Q}_2$$

$$\mathcal{E}_{121} = \hat{P} \hat{A}_{h1} - \hat{\Theta}_1 + \hat{Y}_1^t$$

$$\mathcal{E}_{122} = \hat{P} \hat{A}_{h2} - \hat{\Theta}_2 + \hat{Y}_2^t$$

$$\mathcal{E}_{221} = -\hat{Y}_1 - \hat{Y}_1^t - \hat{Q}_1$$

$$\mathcal{E}_{332} = -\hat{Y}_2 - \hat{Y}_2^t - \hat{Q}_2$$

**Closed Loop:**

So, the plant is stable and tracks the model for  $0 < \hat{P} = \hat{P}^t, 0 < \hat{Q}_1 = \hat{Q}_1^t,$

$0 < \hat{Q}_2 = \hat{Q}_2^t, \quad 0 < \hat{W}_{i1} = \hat{W}_{i1}^t, 0 < \hat{W}_{i2} = \hat{W}_{i2}^t, \quad \& \hat{\theta}_1 \in \Re^{n \times n}, \hat{\theta}_2 \in \Re^{n \times n}, \hat{Y}_1 \in \Re^{n \times n}, \hat{Y}_2 \in \Re^{n \times n}$  and the new LMI is satisfied:

$$(4.45) \quad \begin{bmatrix} \mathcal{E}_{11a} & \mathcal{E}_{121a} & \mathcal{E}_{122a} & \tau_1 \theta_1 & \tau_2 \theta_2 & \hat{M} \hat{F}_o & \hat{M} \hat{G}_o^t & -\tau_1 \hat{M} A^t & -\tau_2 \hat{M} A^t \\ \bullet & \mathcal{E}_{221a} & 0 & -\tau_1 \hat{Y}_1 & 0 & 0 & \hat{M} \hat{G}_{do1}^t & -\tau_1 \hat{M} A_{h1}^t & -\tau_2 \hat{M} A_{h1}^t \\ \bullet & \bullet & \mathcal{E}_{332a} & 0 & -\tau_2 \hat{Y}_2 & 0 & \hat{M} \hat{G}_{do2}^t & -\tau_1 \hat{M} A_{h2}^t & -\tau_2 \hat{M} A_{h2}^t \\ \bullet & \bullet & \bullet & -\tau_1 \hat{W}_{i1} & 0 & 0 & 0 & 0 & 0 \\ \bullet & \bullet & \bullet & \bullet & -\tau_2 \hat{W}_{i2} & 0 & 0 & 0 & 0 \\ \bullet & \bullet & \bullet & \bullet & \bullet & -\gamma^2 I & \hat{\Phi}_o^t & -\tau_1 \hat{F}_o^t & -\tau_2 \hat{F}_o^t \\ \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & -I & 0 & 0 \\ \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & -\tau_1 \hat{W}_{i1} & 0 \\ \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & -\tau_2 \hat{W}_{i1} \end{bmatrix} < 0$$

where:

$$\mathcal{E}_{11} = \hat{M} \hat{A} + \hat{A}^t \hat{M} - \hat{B} \hat{Y} - \hat{Y}^t \hat{B}^t + \hat{\theta}_1 + \hat{\theta}_1^t + \hat{\theta}_2 + \hat{\theta}_2^t + \hat{Q}_1 + \hat{Q}_2$$

$$\hat{Y} = K \hat{M}$$

$$\mathcal{E}_{121a} = \hat{M} \hat{A}_{h1} - \hat{\theta}_1 + \hat{Y}_1^t$$

$$\mathcal{E}_{122a} = \hat{M} \hat{A}_{h2} - \hat{\theta}_2 + \hat{Y}_2^t$$

$$\mathcal{E}_{221a} = -\hat{Y}_1 - \hat{Y}_1^t - \hat{Q}_1$$

$$\mathcal{E}_{332a} = -\hat{Y}_2 - \hat{Y}_2^t - \hat{Q}_2$$

$$\hat{W}_{i1} = \hat{W}_1^{-1}$$

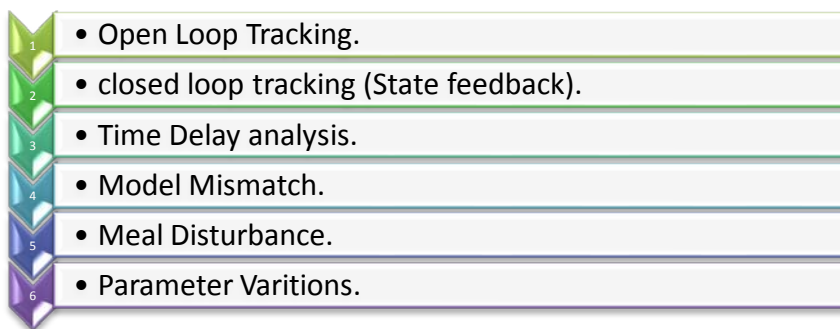
$$\hat{W}_{i2} = \hat{W}_2^{-1}$$

## CHAPTER 5

### RESULTS & ANALYSIS

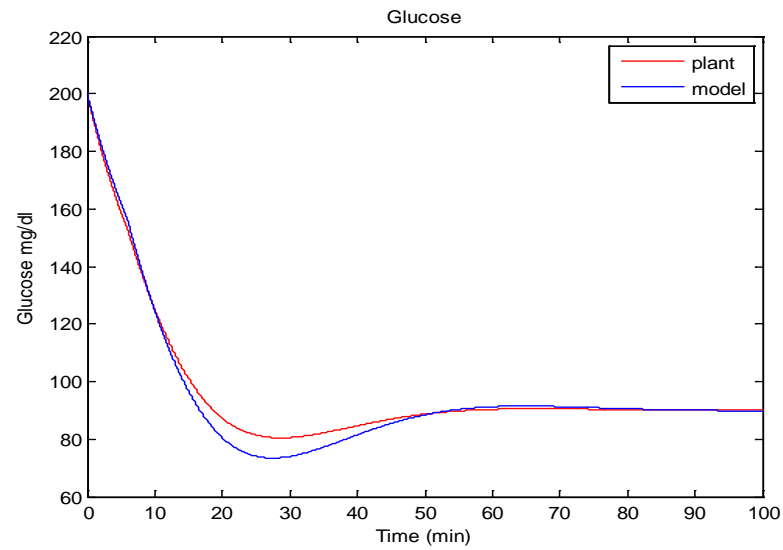
#### 5.1. Linear Simulation:

This chapter will show the results of the derived LMI in the treatment of diabetes patients and it will discuss and analyze the results and their possibility to be applied in medical practice. In this part we will use the linearized model in simulation for testing. Six main issues will be discussed here to evaluate the performance of the controller.

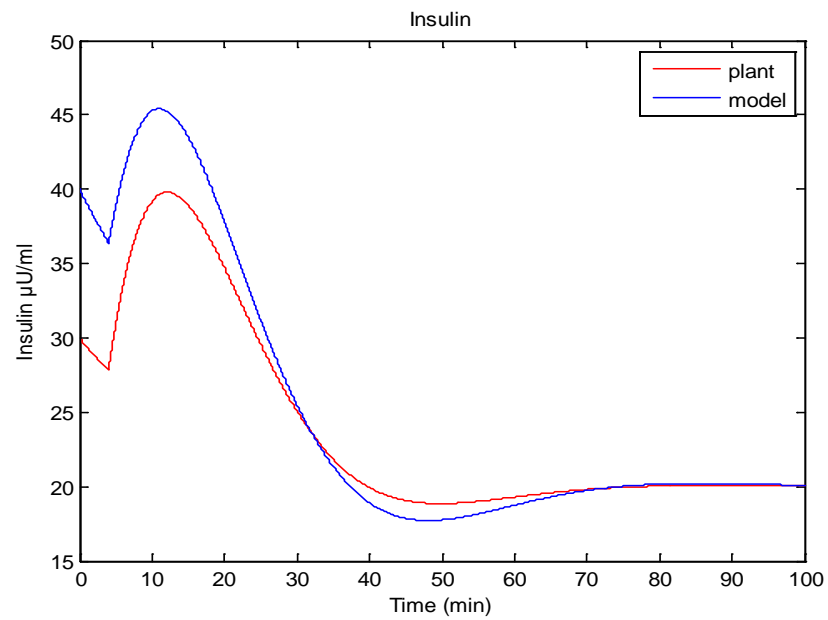
- 
- 1 • Open Loop Tracking.
  - 2 • closed loop tracking (State feedback).
  - 3 • Time Delay analysis.
  - 4 • Model Mismatch.
  - 5 • Meal Disturbance.
  - 6 • Parameter Varitions.

##### 5.1.1. Stability Analysis:

In this section, we will show how the plant track the model (without state feedback control)



**Figure 5.7: Glucose Response.**

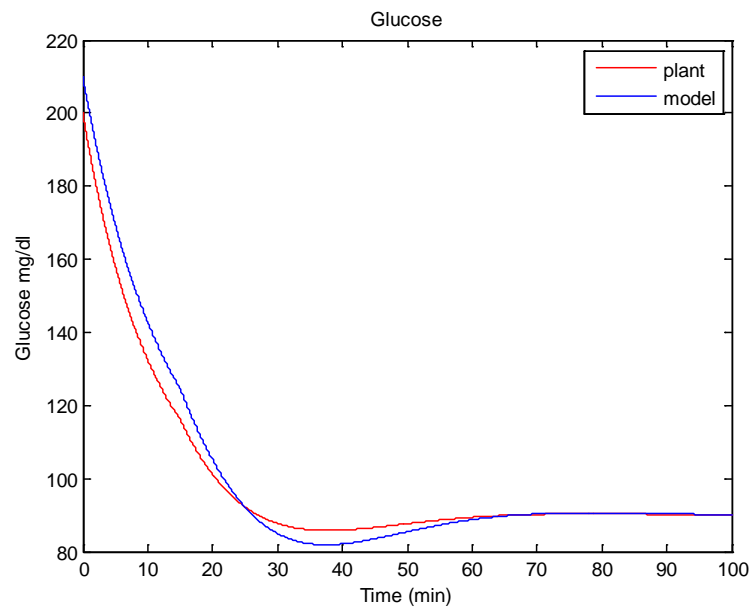


**Figure 5.8 : Insulin Response.**

This figure shows the open loop response for both glucose and insulin due to initial condition.

We can notice the effect of two time delay (the first one in insulin figure at  $t = 6$  min and the second one in glucose response at  $t = 10$  min). It is clear that the plant succeeds in tracking the dynamic of the model with minimum error.

### 5.1.2. State feedback control



**Figure 5.9: Glucose Response with state feedback control.**



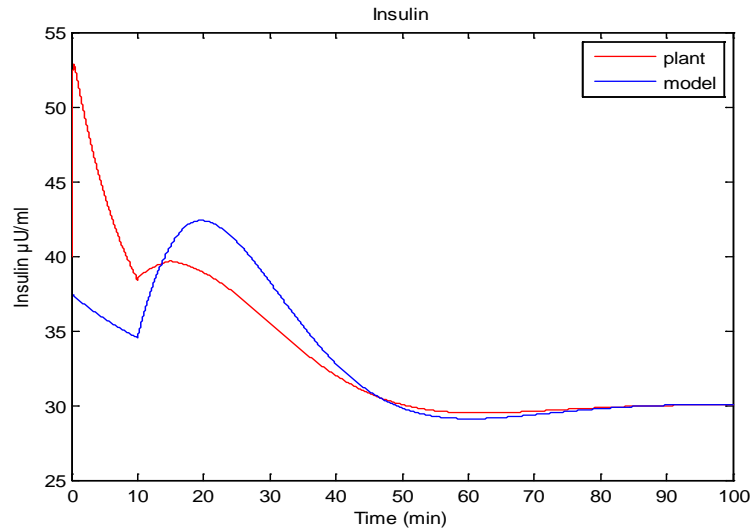


Figure 5.10: Insulin Response with state feedback control.

(1) Gain = [0.1242 -10.9445 -0.1193 9.0253].

(2) Gama = 0.8566.

We notice here that the controller can stabilize the plant and force it to track the dynamic of the model with a begging reasonable gain and rejection ratio. Also, we notice that the second state (insulin) increases.

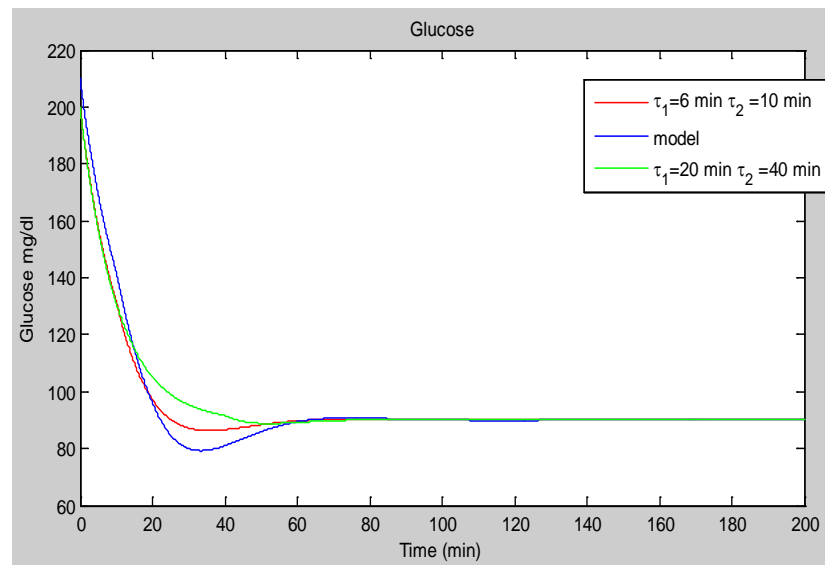
### 5.1.3. Time Delay Analysis:

In this section we will do the analysis for two issues:

- A. We use constant uncertain bounded time delay, and the maximum time delays  $\tau_1 = 20$  min and  $\tau_2 = 40$  min. To show this assumption is valid, we will test the control design based on the maximum time delay.
- B. We will test time delay variations with respect to the nominal time delay on which the control design is based (robustness analysis).

**Part A:****Table 5.4: Gain & Rejection Ratio Comparison for time delay change.**

Case	Gain (K)	Gama ( $\gamma$ )
$\tau_1 = 6 \text{ min and } \tau_2 = 10 \text{ min}$	0.1038 -6.6834 -0.1022 4.8854	0.8343
$\tau_1 = 20 \text{ min and } \tau_2 = 40 \text{ min}$	0.4168 -14.9944 0.0267 14.4645	0.9626

**Figure 5.11: Glucose Response due to Time delay change.**

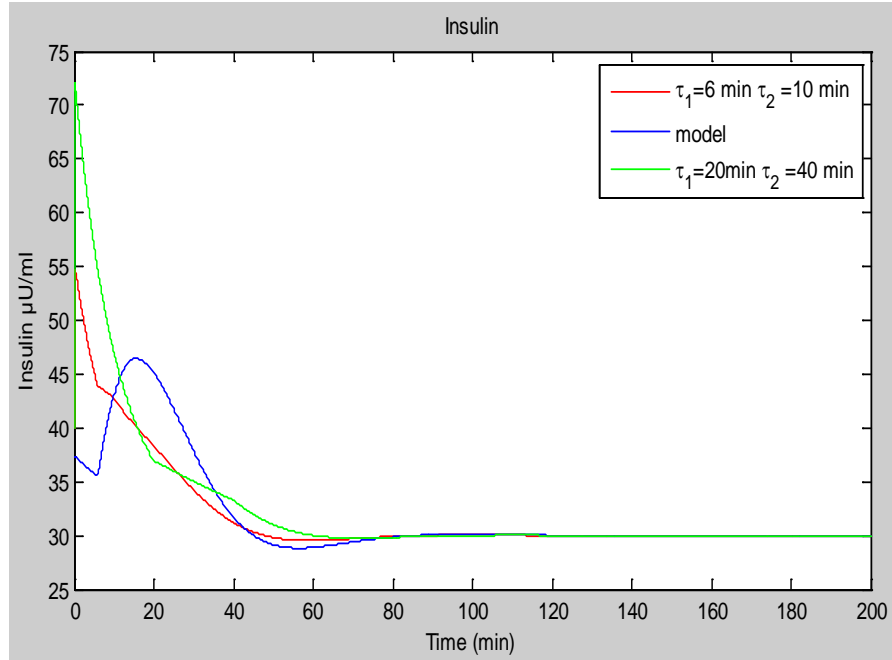


Figure 5.12: Insulin Glucose Response due to Time delay change

Table 5.5: : Accuracy Analysis due to Time delay change.

Case	max error	mean error
$\tau_1 = 6 \text{ min}, \tau_2 = 10 \text{ min}$	G: 10.1157mg/dl	G: -0.2469mg/dl
	I: 8.2795μU/ml	I: 1.8777 μU/ml
$\tau_1 = 20 \text{ min and } \tau_2 = 40 \text{ min}$	G: 10.1762mg/dl	G: 1.7874mg/dl
	I: 8.2795 μU/ml	I: 1.3548 μU/ml

We notice that as time delay increases:

1. The gain  $K$  increases.
2. Rejection ratio  $\gamma$  increases.

3. The response will be slower and it takes more time to reach steady-state value.
4. Comparing the error the two cases, we notice this maximum of the error is almost the same. This is a good point because, as the time delay increases, the controlled variable (Glucose) and insulin do not go beyond the physical range.

However, the system is still able to stabilize the plant which shows that our assumption on type of used time delay is valid for our case.

## Part B:

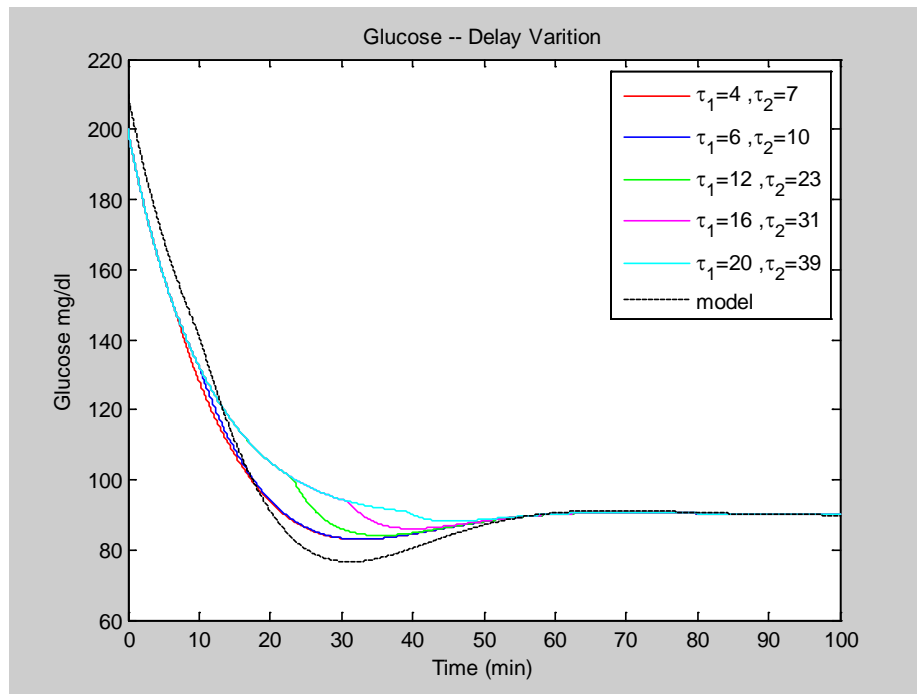
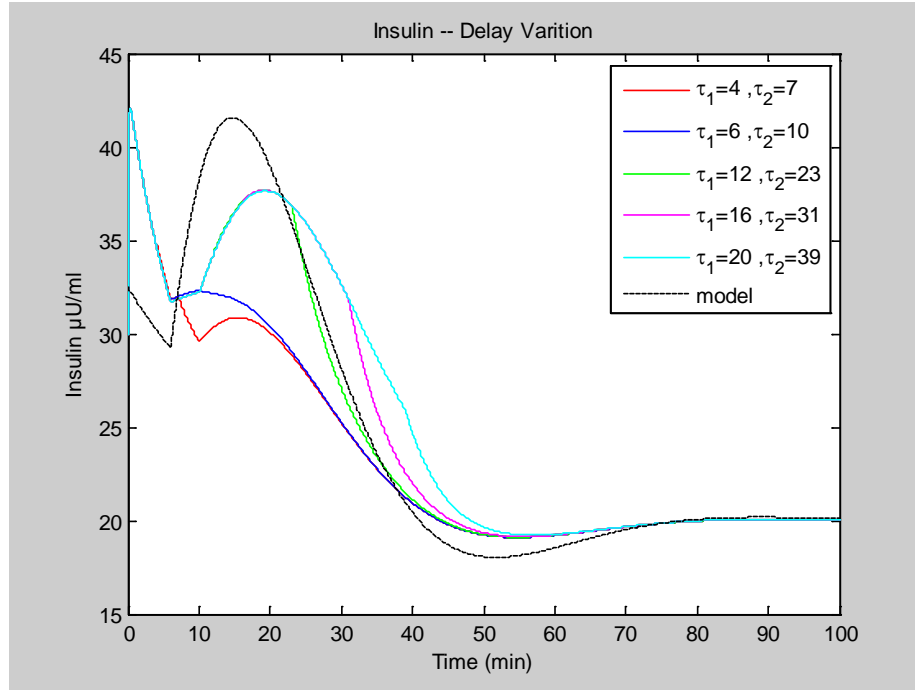


Figure 5.13: Glucose Response due to Time delay variations (Robustness analysis).



**Figure 5.14: Insulin Response due to Time delay variations (Robustness analysis).**

We can notice that, as the time delay increases, the dynamic of the system becomes slower and it takes more time to reach to the steady-state value, and we can notice the effect of the two time delays on insulin clearly as the delay becomes larger.

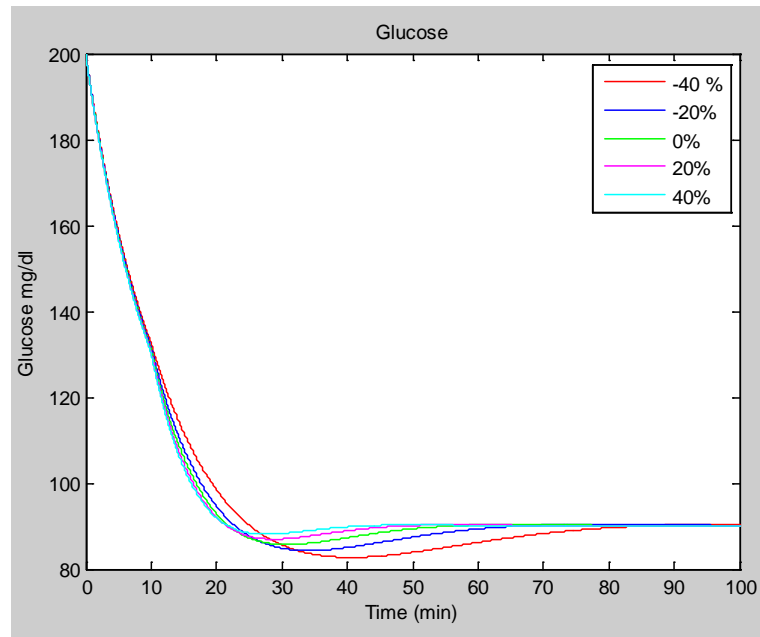
#### 5.1.4. Model Mismatch:

In this section, we change the dynamic speed of the model (by changing the eigenvalues by a certain percentage) and we see the effect on the plant. In other words,  $A_m = (A_p + d \cdot A_p)$ .

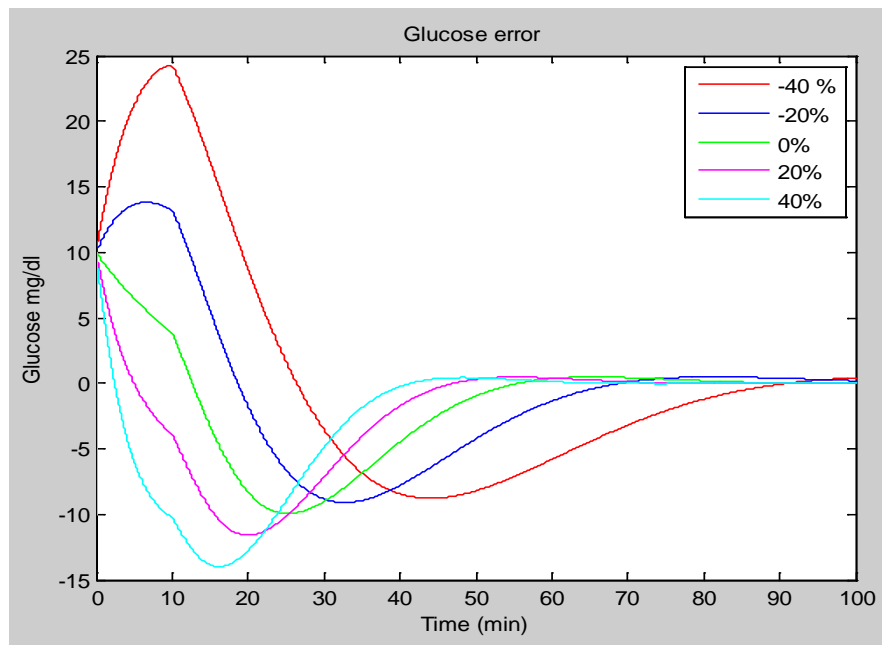
**Table 5.6: Gain and rejection ratio rejection for model mismatch.**

Delta	Gain (K)				Gama
-20 %	0.0427	-8.9424	-0.0946	4.1549	0.7813
-40 %	0.0902	-7.7323	-0.0855	4.3060	0.8310
0%	0.1155	-7.1069	-0.0836	4.6569	0.8337
20 %	0.1348	-6.5382	-0.0808	5.0070	0.8345
40 %	0.1514	-6.0301	-0.0768	5.3797	0.8349

**(a) Glucose response:**

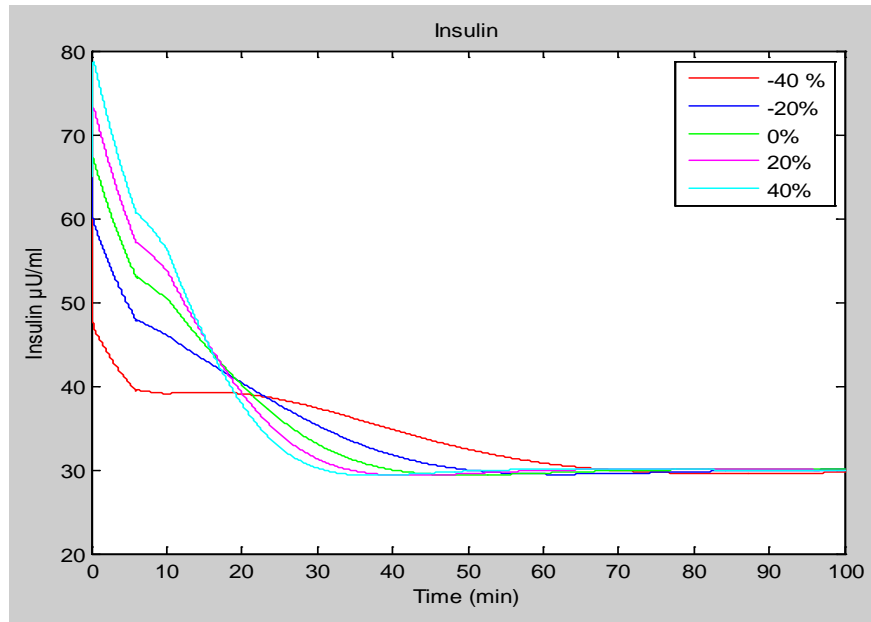


**Figure 5.15: Glucose Response for various reference models selection.**

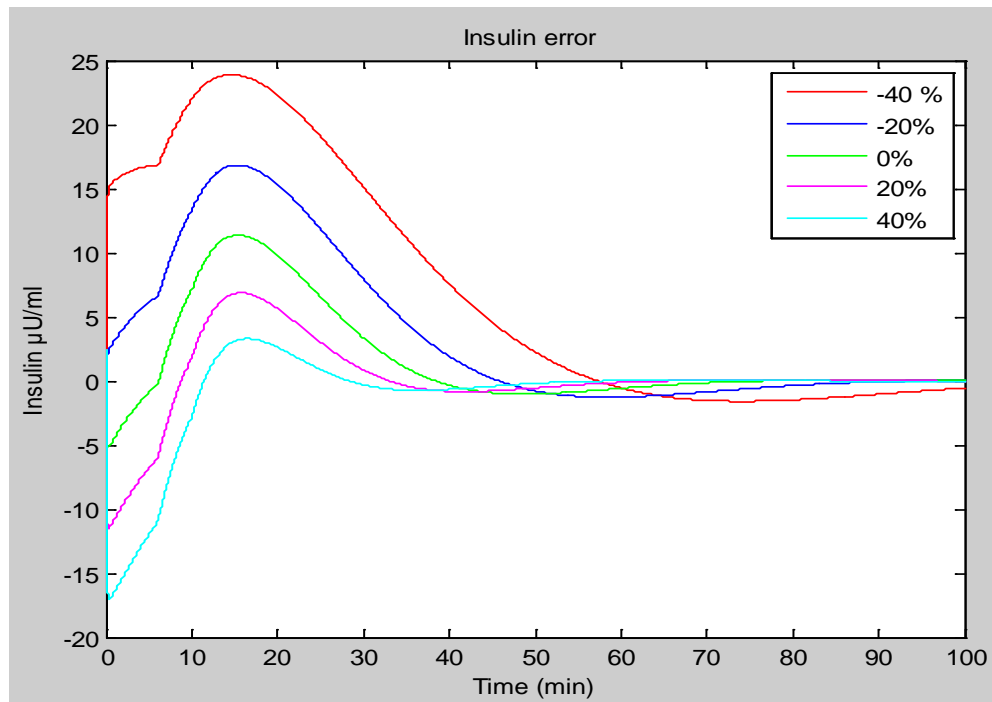


**Figure 5.16: Glucose error for various reference models selection.**

**b) Insulin:**



**Figure 5.17: Insulin response for various reference models selection.**



**Figure 5.18: Insulin error for various reference models selection.**

There, as the difference between dynamic speed of the plant and model (the magnitude of their eigenvalue) increase the error also increases and the controller takes more time to stabilize the system and to reach steady-state value. Also, as the difference becomes larger, the required gain and rejection ratio increases accordingly. So, the selection of the model affects the performance of the controller mainly in terms of transient error.

### **5.1.5. Meal Disturbance:**

One of the important issues which several controllers failed to overcome is the meal disturbance. In fact, overcoming this problem is difficult because of the following reasons:

1. People usually eat several meals at different periods and with mixed content (carbohydrate, meat, fat, vegetables.....).
2. These meals contain several types of glucose (simple – compound).
3. The digestion and absorbing of these sugar types vary in terms of time and methodology.
4. Patient's situation, activity, age, health have a significant effect on the glucose level in the patient's blood.
5. Some of the sugar is converted and stored as fat in the cells.

The normal situation is for the glucose level to be in the range 70-110 mg/dl (normalglycemia) and the acceptable range is in the range 60-140 mg/dl. In fact, even in



the normal person, the glucose level can exceed this range, but the pancreas can overcome this situation by injecting insulin into the blood.

The disturbance can be positive (meal disturbance) or negative due to different reasons which make the glucose level drop below the desired level.

Let us test different levels of disturbance at different periods and check the maximum level that the controller can sustain with the following procedure:

**Two disturbances** are inserted, the former is in transient zone, and the latter is in steady-state zone, and each of them is of period 500 sample.

**(1) 200 mg per sample ( $200 \times 500 \text{ mg} = 100 \text{ g}$ ) of glucose.**

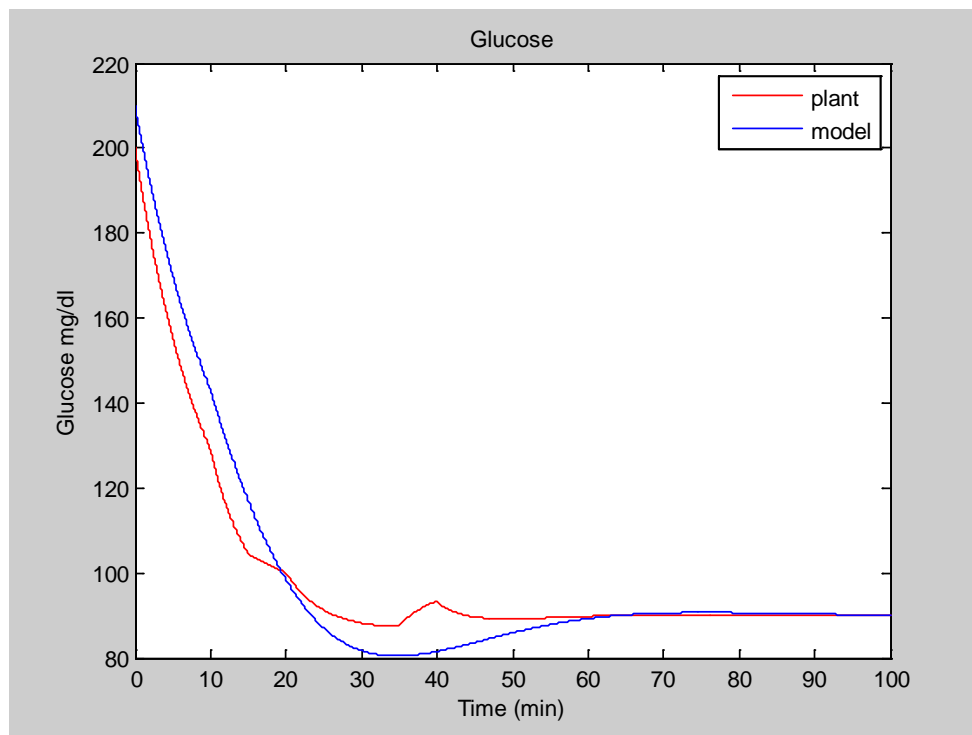


Figure 5.19: Glucose Response due to 100 g of meal disturbance.

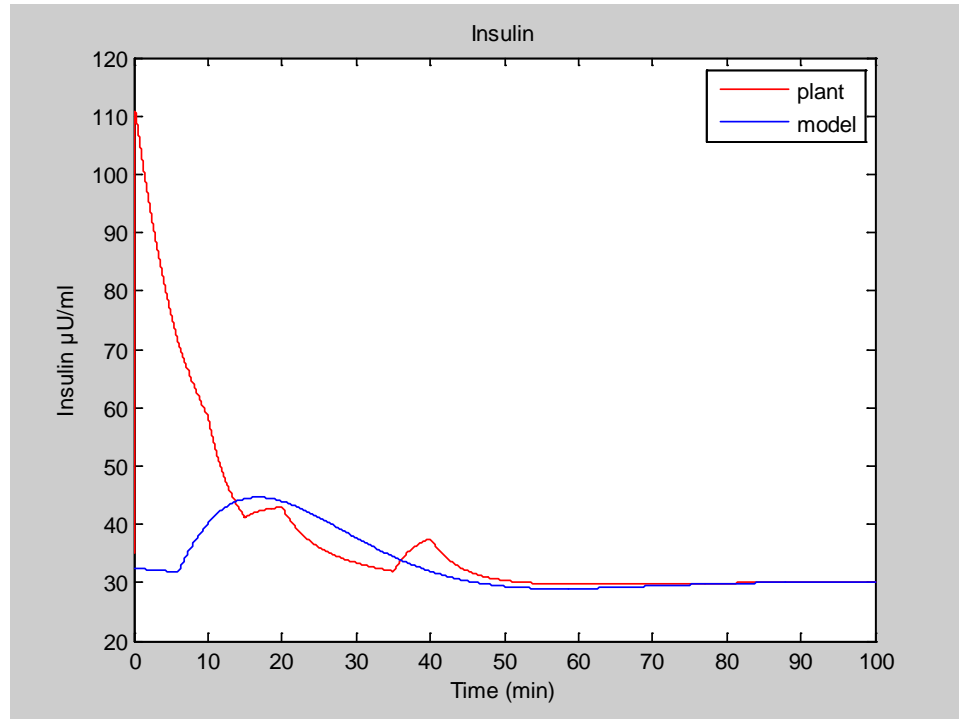


Figure 5.20: Insulin Response due to 100 g of meal disturbance.

(2) 400 mg per sample ( $400 \times 500 \text{ mg} = 200 \text{ g}$ ) of glucose:

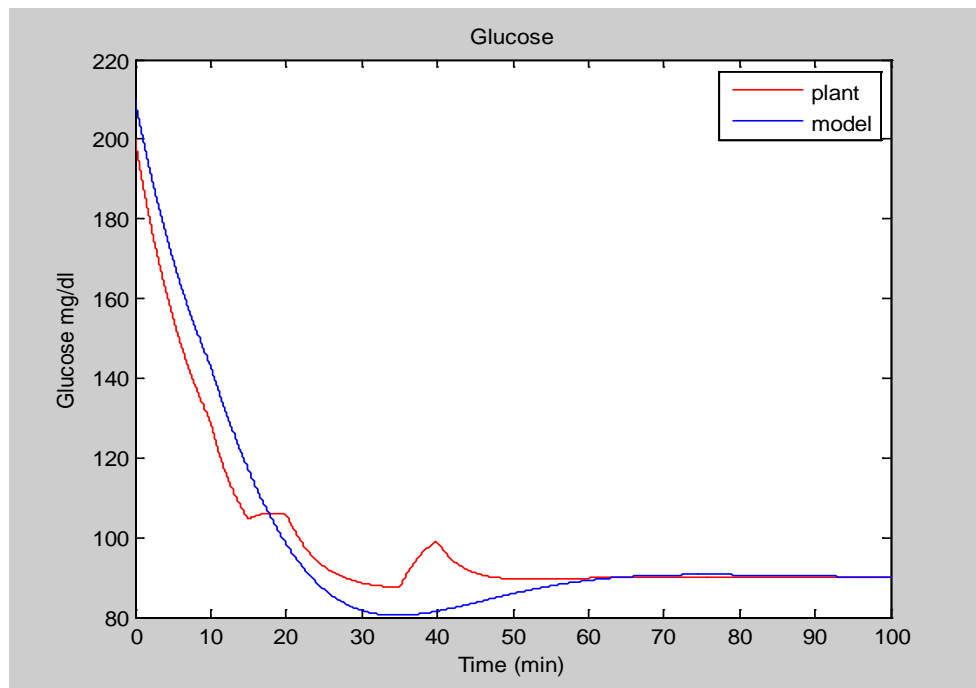


Figure 5.21: Glucose Response due to 200 g of meal disturbance.

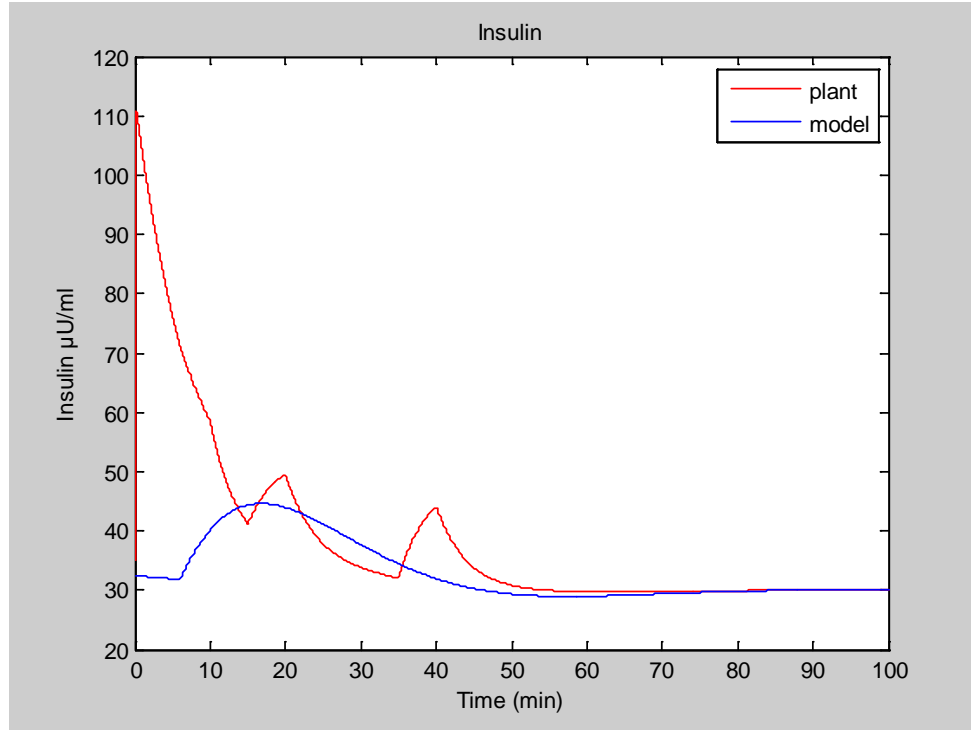


Figure 5.22: Insulin Response due to 200 g of meal disturbance.

(3) 800 mg per sample ( $800 \times 500 \text{ mg} = 400 \text{ g}$ ) of glucose:

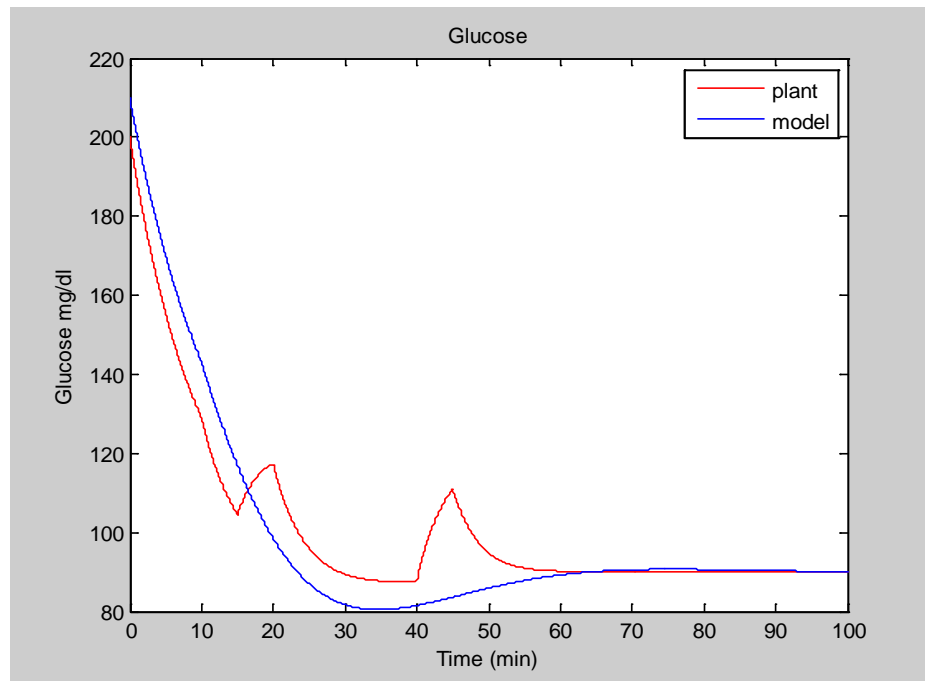


Figure 5.23: Glucose Response due to 400 g of meal disturbance.

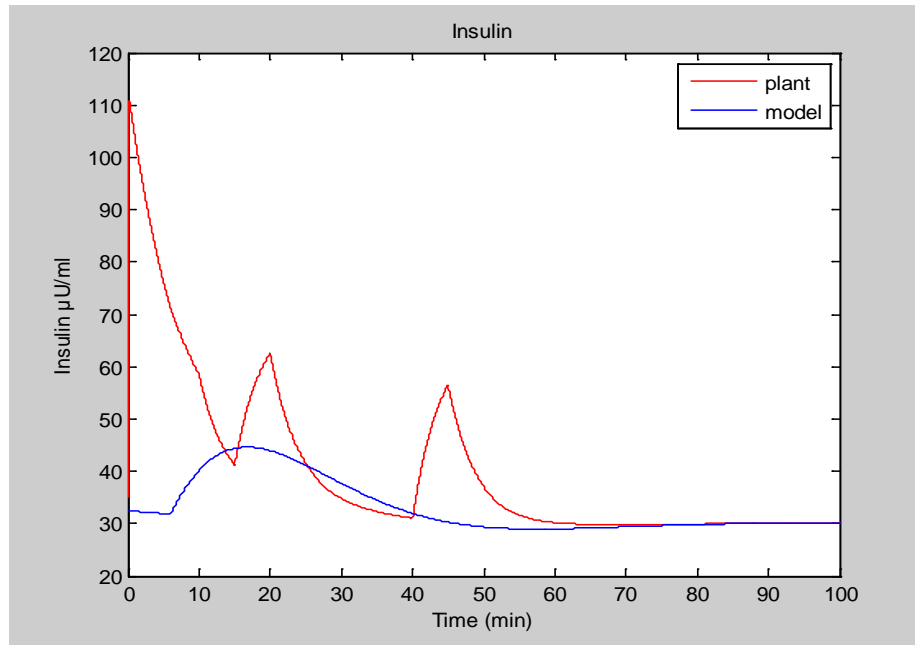


Figure 5.24: Insulin Response due to 400 g of meal disturbance.

(4) 1600 mg per sample ( $1600 \times 500 \text{ mg} = 800 \text{ g}$ ) of glucose:

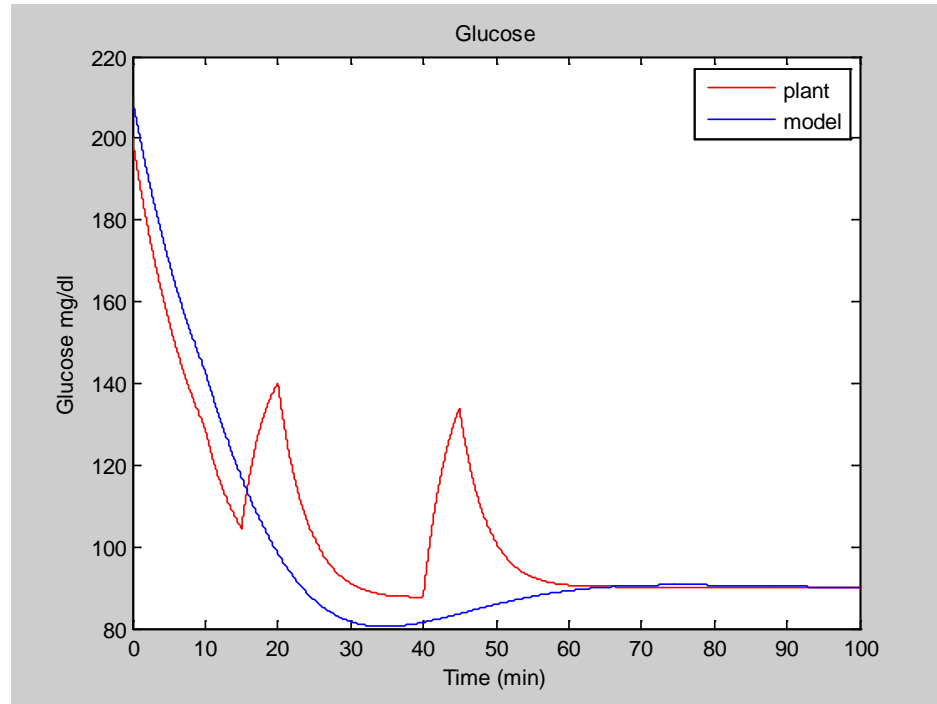


Figure 5.25: Glucose Response due to 800 g of meal disturbance.

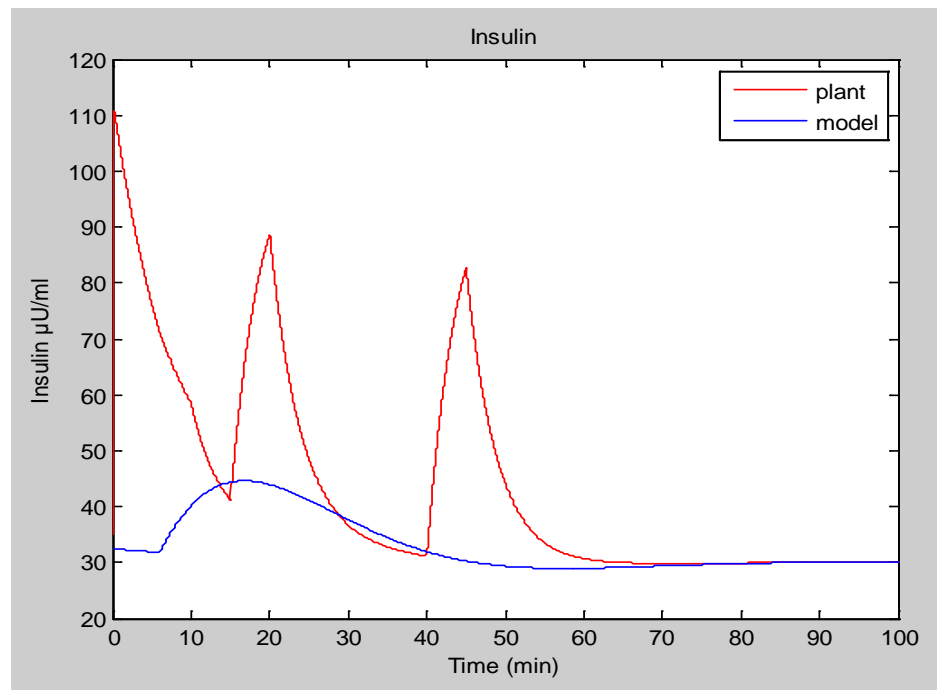


Figure 5.26: Insulin Response due to 800 g of meal disturbance.

(5) 2600 mg per sample ( $1600 \times 500 \text{ mg} = 1300 \text{ g} = 1.3 \text{ KG}$ ) of glucose:

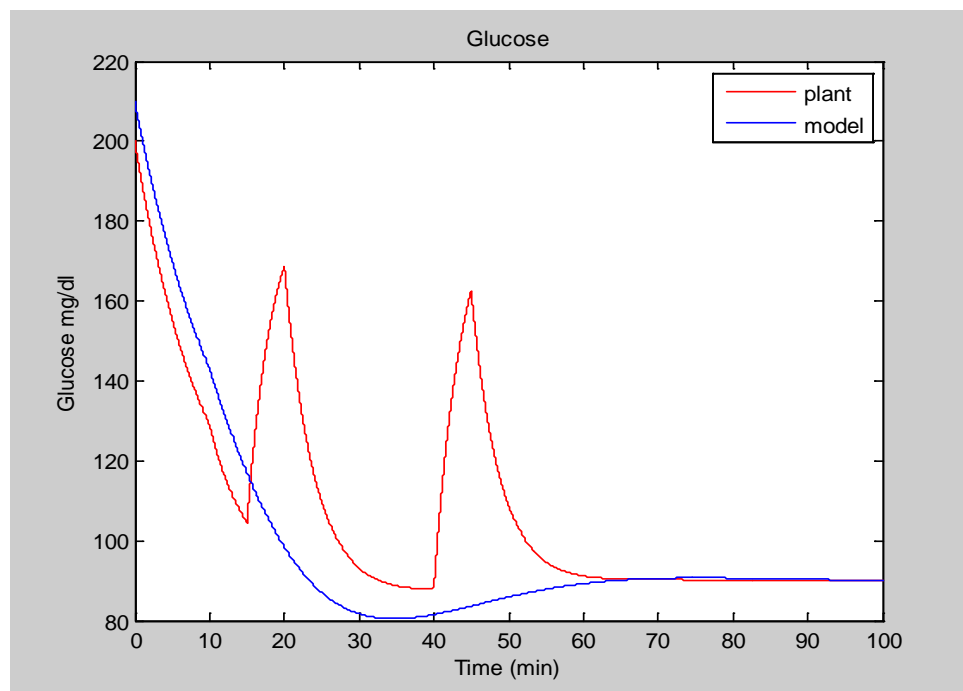


Figure 5.27: Glucose Response due to 1.3 kg of meal disturbance.

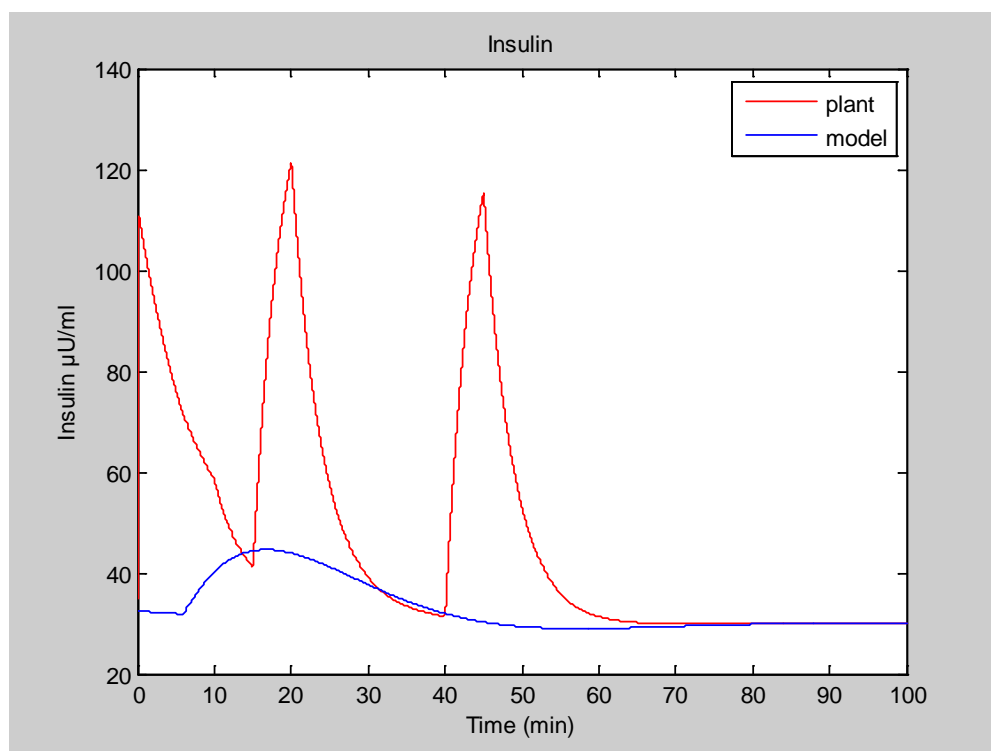


Figure 5.28: Insulin Response due to 1.3 kg of meal disturbance.

Even with large meal disturbance, the controller can stabilize the plant and keep in the acceptable range. Even if it exceeds this range temporarily it returns to the normal range.

The maximum limit for our case is  $800 \text{ g} = 0.8 \text{ Kg}$  of pure glucose which rarely happens in real cases.

The level of glucose increases when the disturbance enters the system because we are using feedback type and we cannot use feedforward techniques because the meal disturbance is difficult to measure. This is done by the pancreas in normal people.

### (B) Negative Disturbances:

(1) 600 mg per sample ( $-600 \times 500 \text{ mg} = -300 \text{ g} = 0.3 \text{ KG}$ ) of glucose:

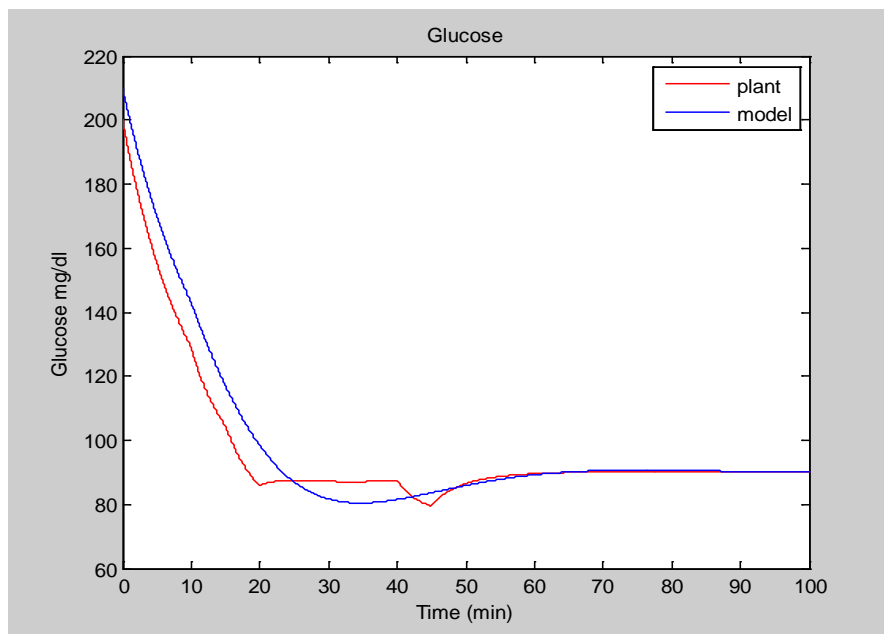
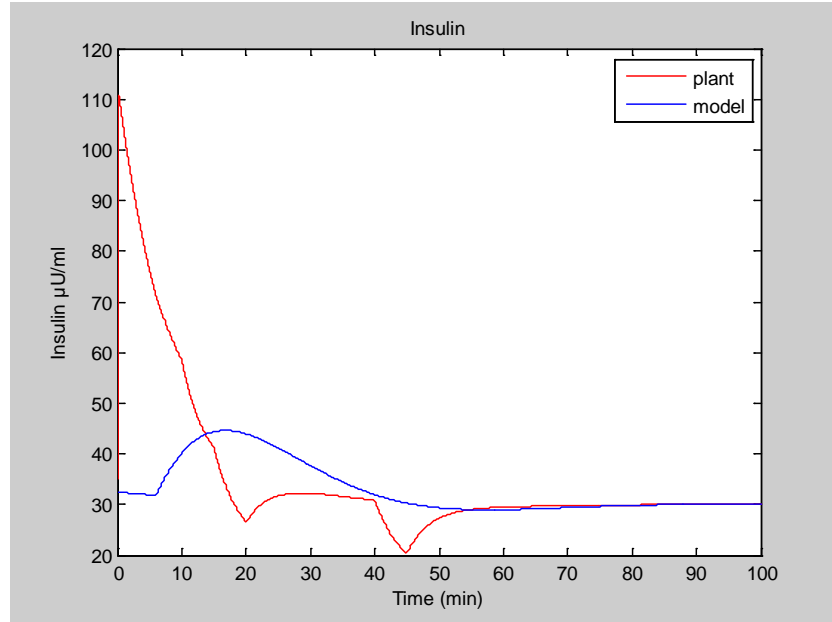


Figure 5.29: Glucose Response due to negative disturbance of 300 g.



**Figure 5.30: Insulin Response due to negative disturbance of 300 g.**

We notice our system reacts to other cases when the glucose level drops, and the level of insulin drops according to the system at the certain level.

This point is important because, as we mentioned before, the control techniques used here or in the other studies consider only the case of hyperglycemia (when the level of glucose increases). So our controller mitigates the effect of glucose's level drop by reducing the level of insulin in the blood.

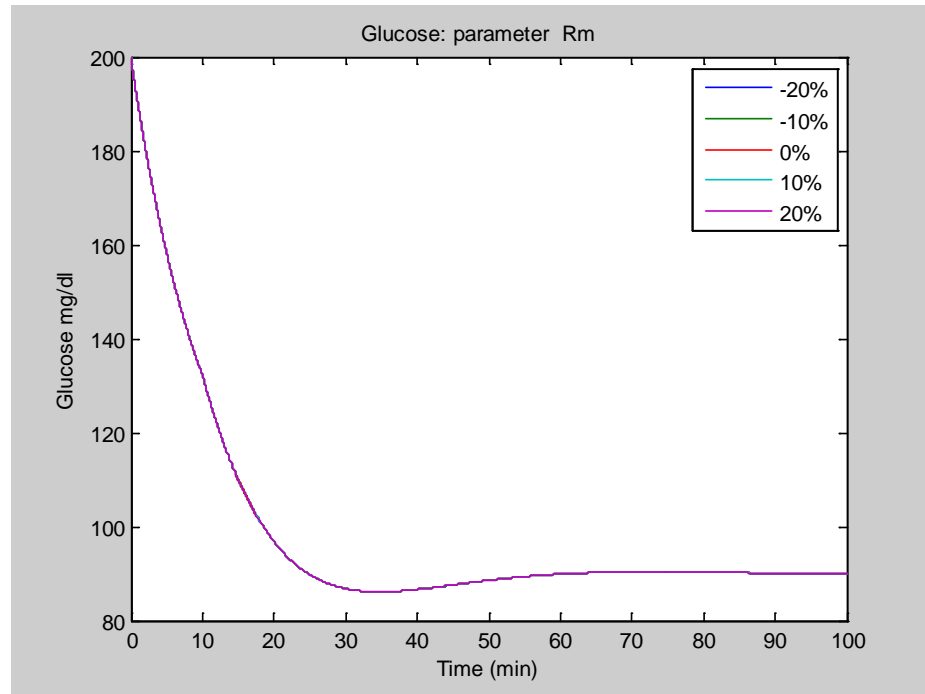
### **5.1.6. Parameter variations**

The parameter values of the two time delay model were identified from experimental data. However, these are nominal values and can vary in the same patient or from one patient to another because of several factors such as age, activity, weight & health of the patient. In this section we will see the effect of the parameter variations of the patient on the performance of the system.

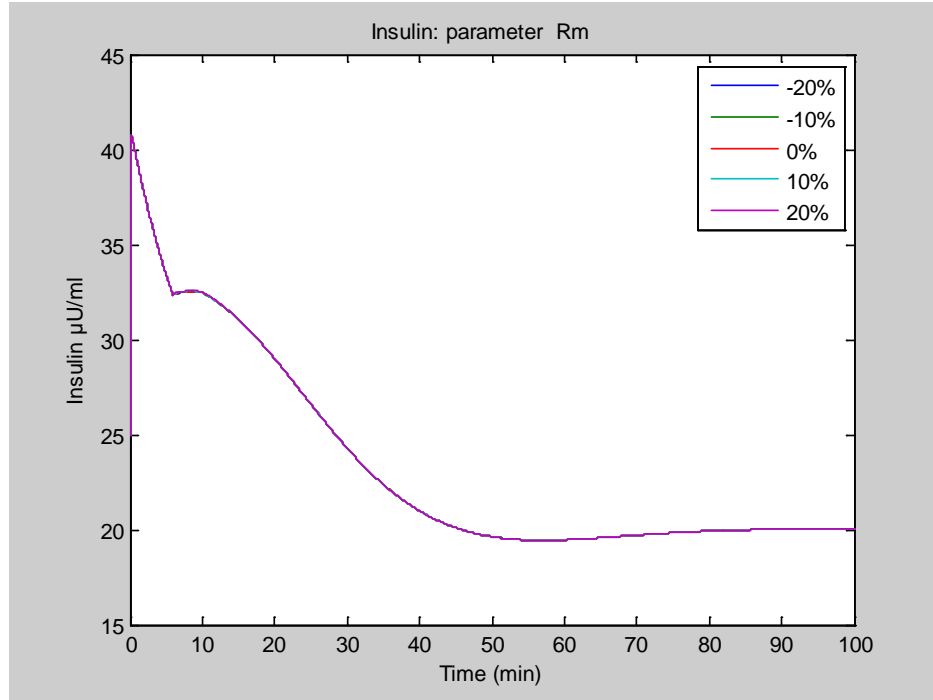


We will change each parameter (the model has 18 parameters) alone to see which of them has a significant effect on performance when it varies.

(1)  $R_m$ :

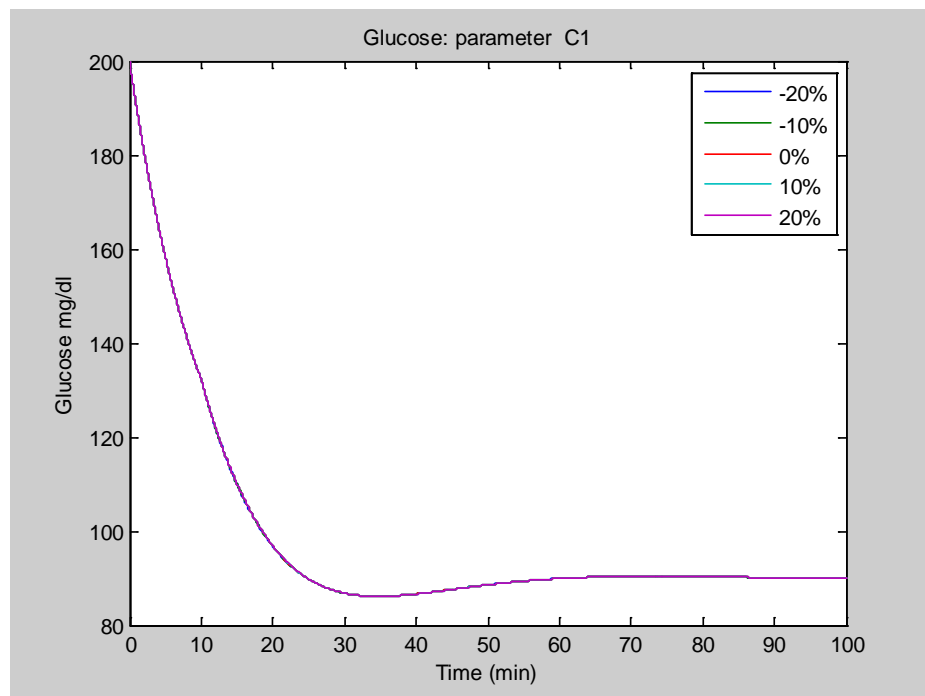


**Figure 5.31: Glucose Response due to variation of parameter  $R_m$ .**



**Figure 5.32: Insulin Response due to variation of parameter  $R_m$ .**

(2)  $C_1$ :



**Figure 5.33: Glucose Response due to variation of parameter  $C_1$ .**

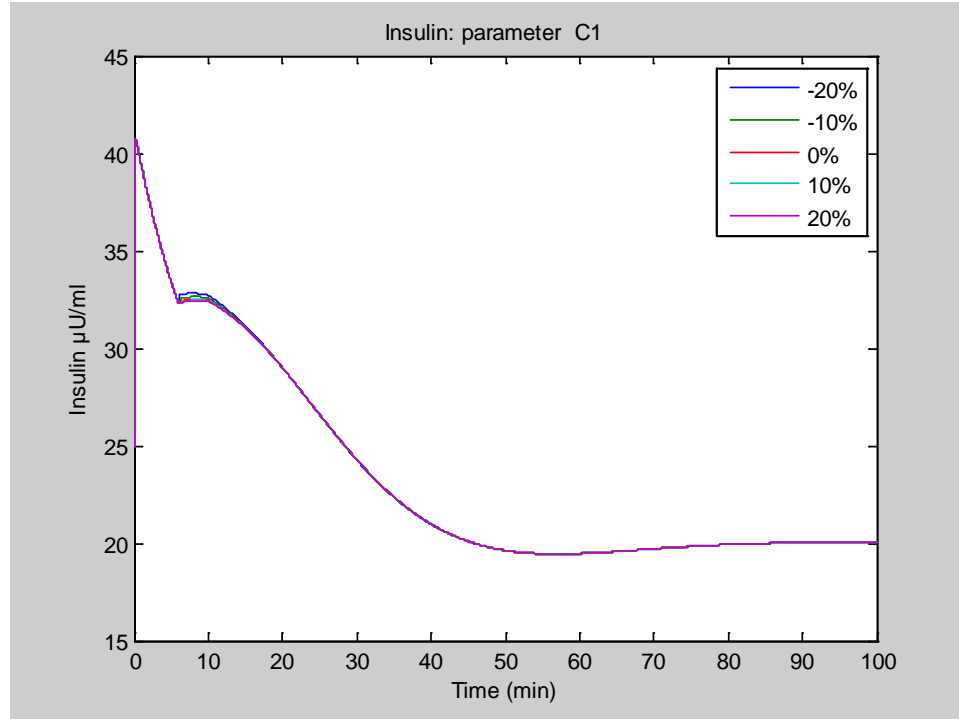


Figure 5.34: Insulin Response due to variation of parameter C1.

(3)  $V_g$ :

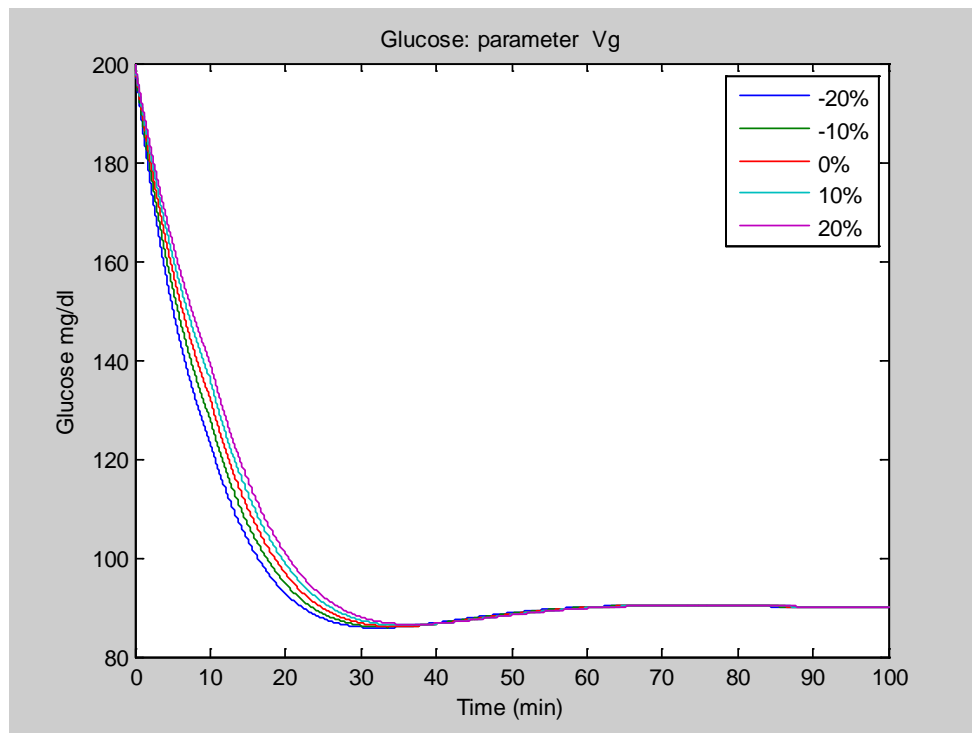


Figure 5.35: Glucose Response due to variation of parameter  $V_g$ .

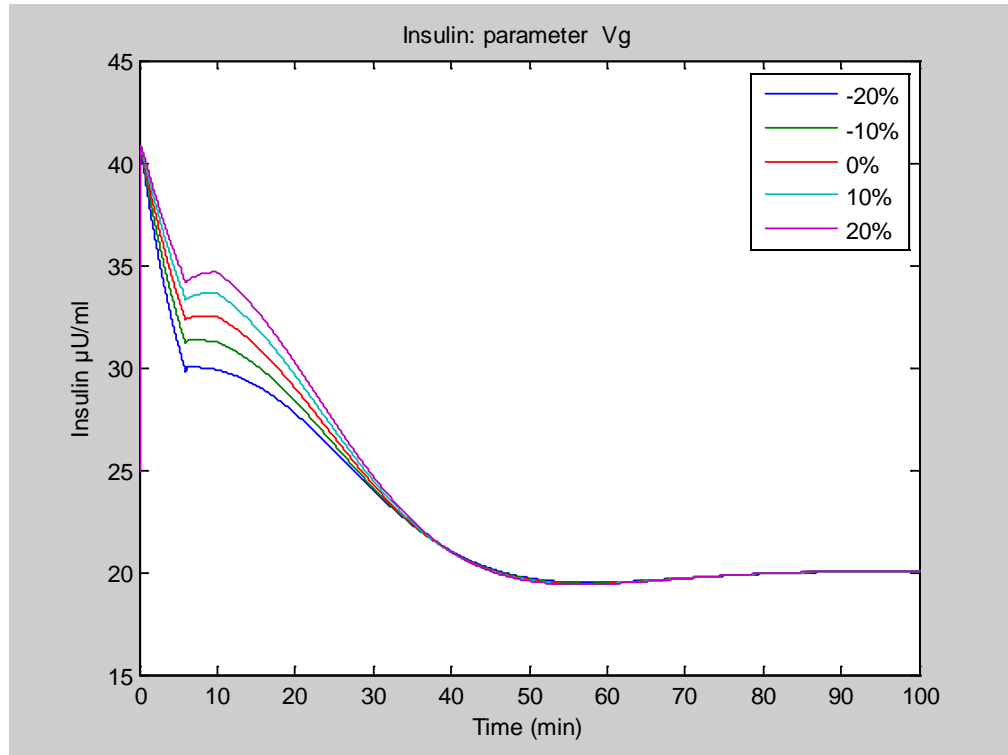


Figure 5.36: Insulin Response due to variation of parameter  $V_g$ .

(4)  $a_1$ :

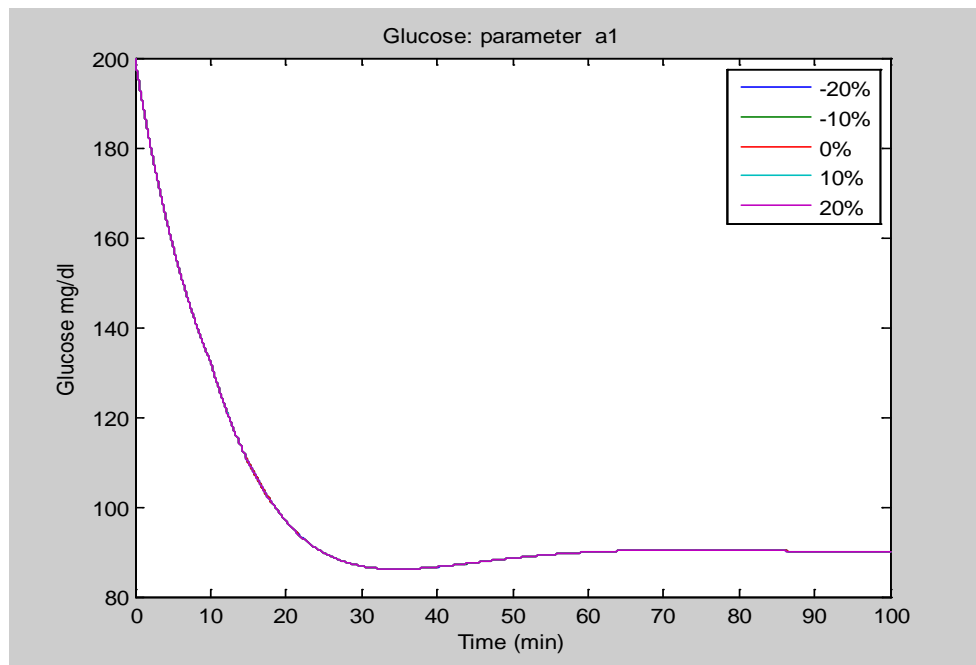


Figure 5.37: Glucose Response due to variation of parameter  $a_1$ .

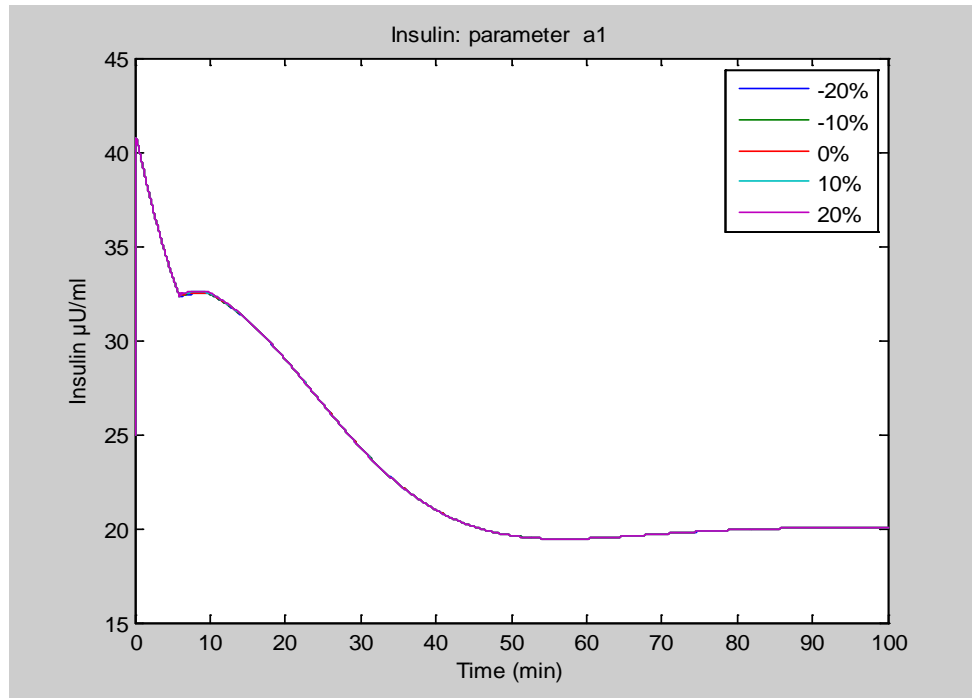


Figure 5.38: Insulin Response due to variation of parameter  $a1$ .

(6)  $U_b$ :

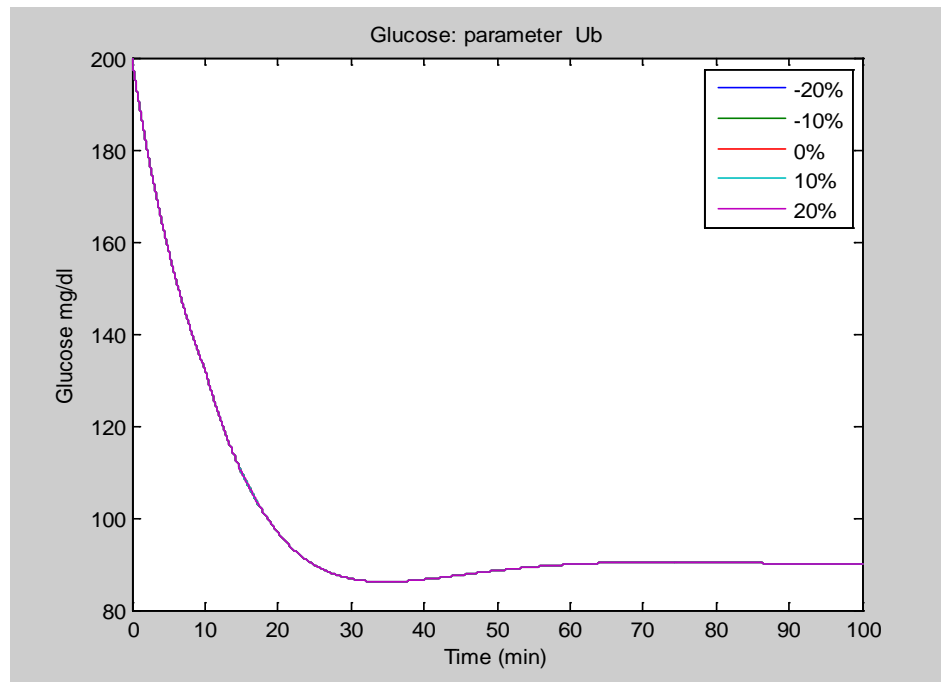


Figure 5.39: Glucose Response due to variation of parameter  $U_b$ .

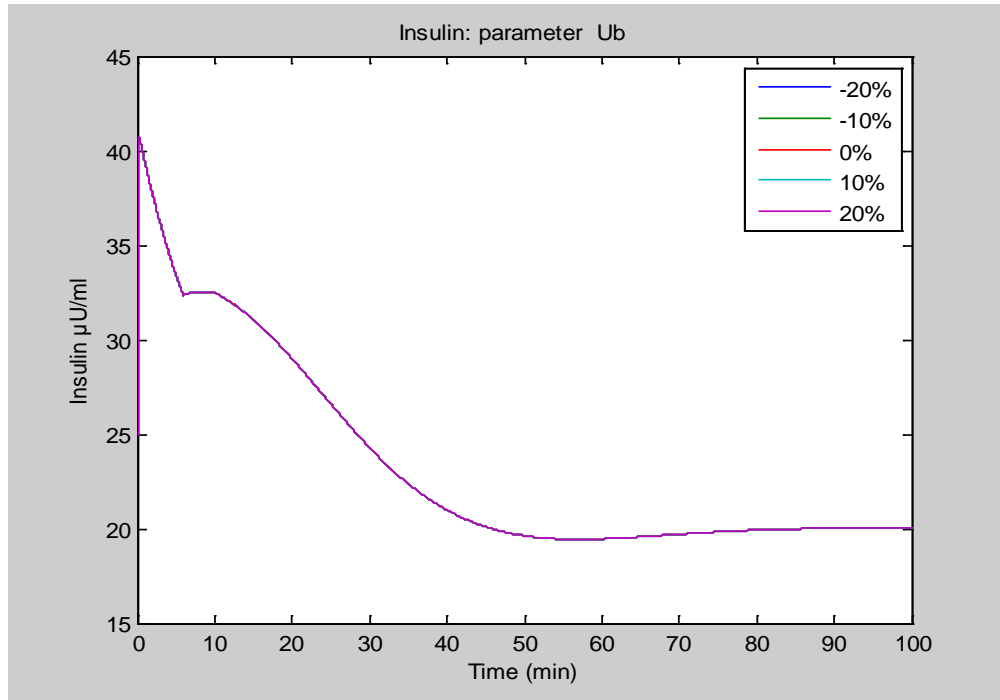


Figure 5.40: Insulin Response due to variation of parameter  $U_b$ .

(7) C2:

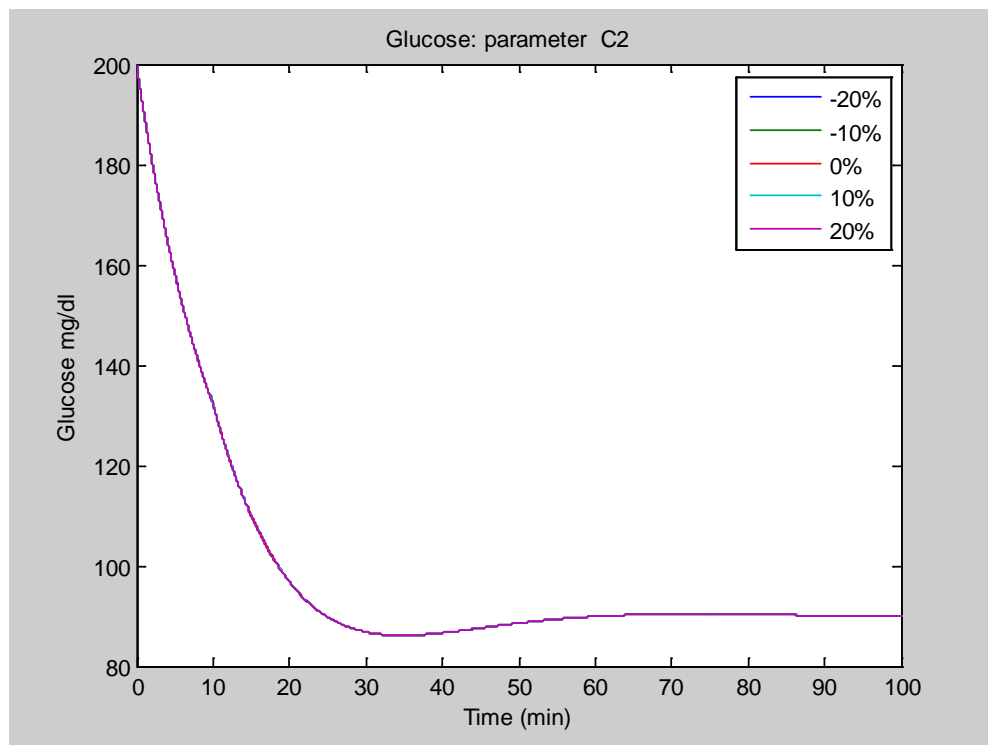
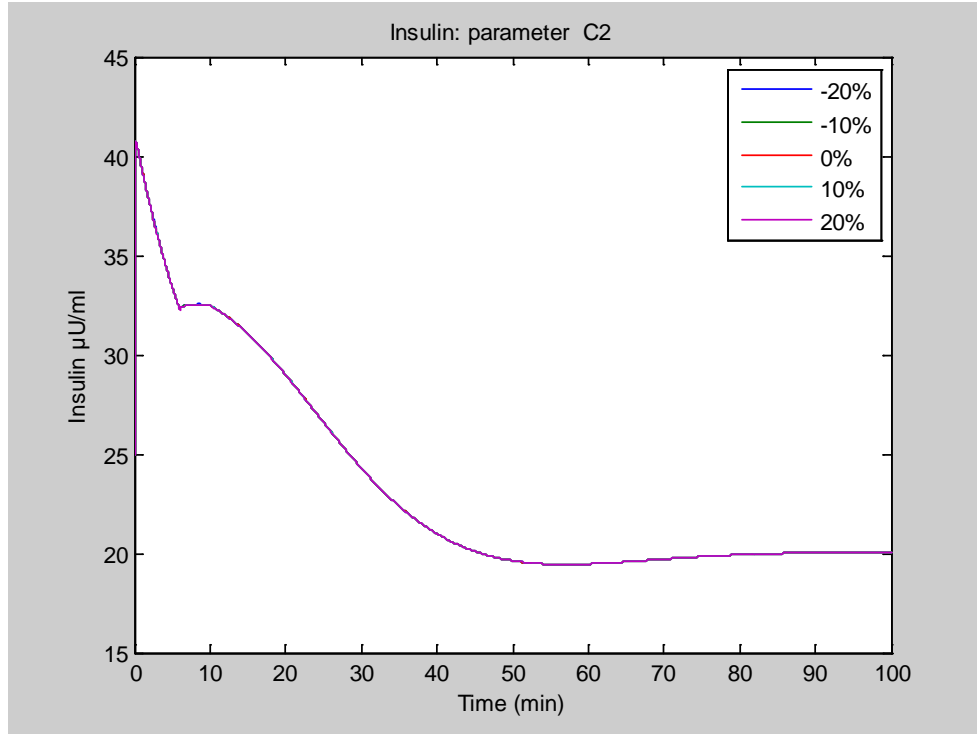


Figure 5.41: Glucose Response due to variation of parameter  $C_2$ .



**Figure 5.42: Insulin Response due to variation of parameter C2.**

(8) C3:

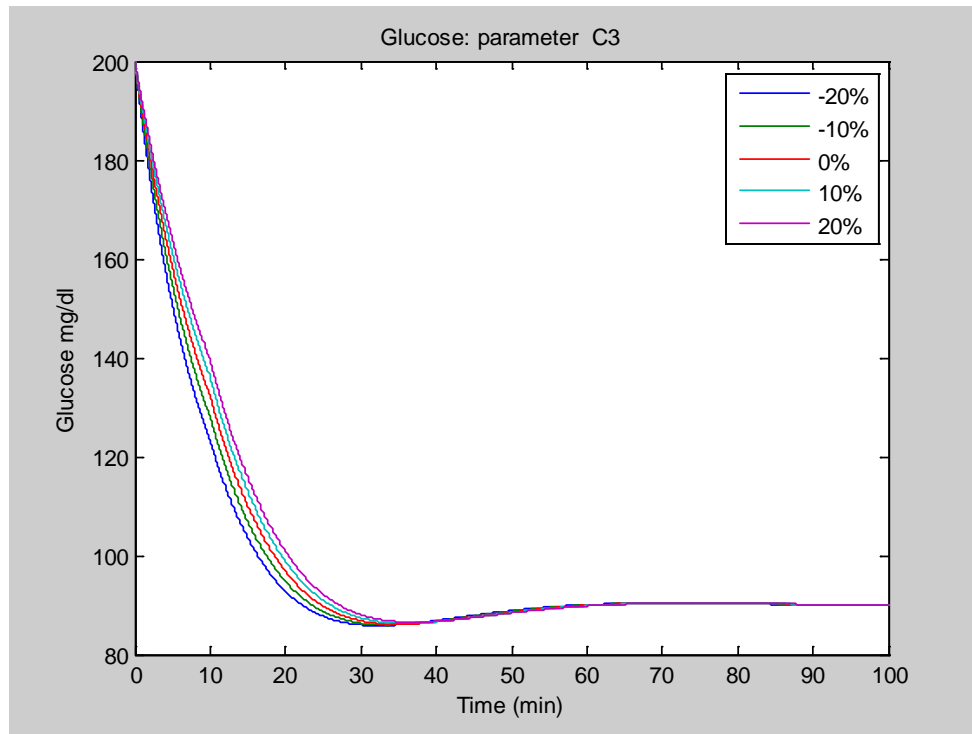


Figure 5.43: Glucose Response due to variation of parameter C3.

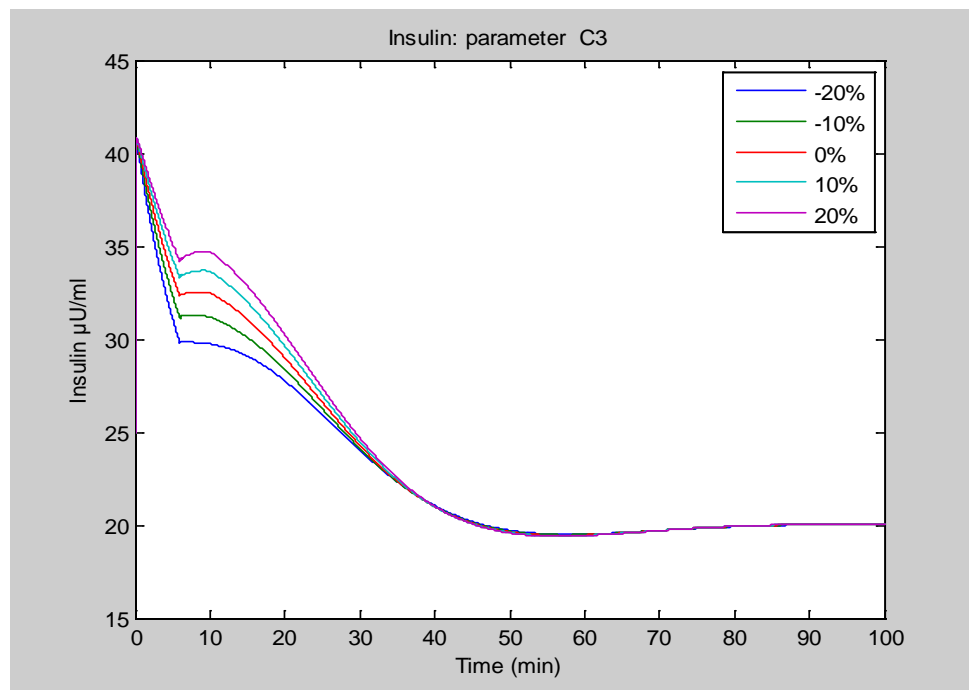


Figure 5.44: Insulin Response due to variation of parameter C3.



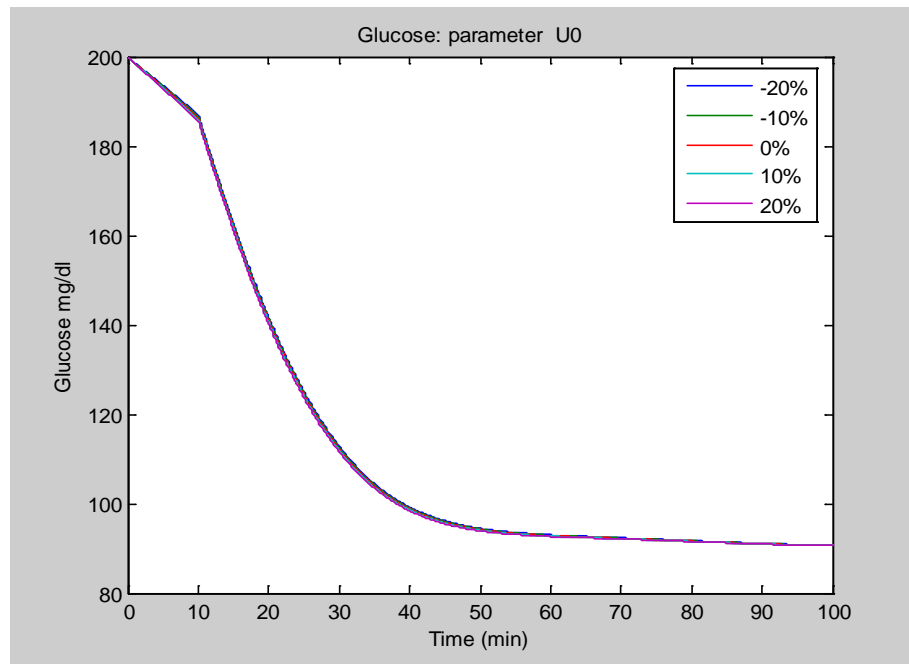
(9)  $U_0$ :

Figure 5.45: Glucose Response due to variation of parameter  $U_0$ .

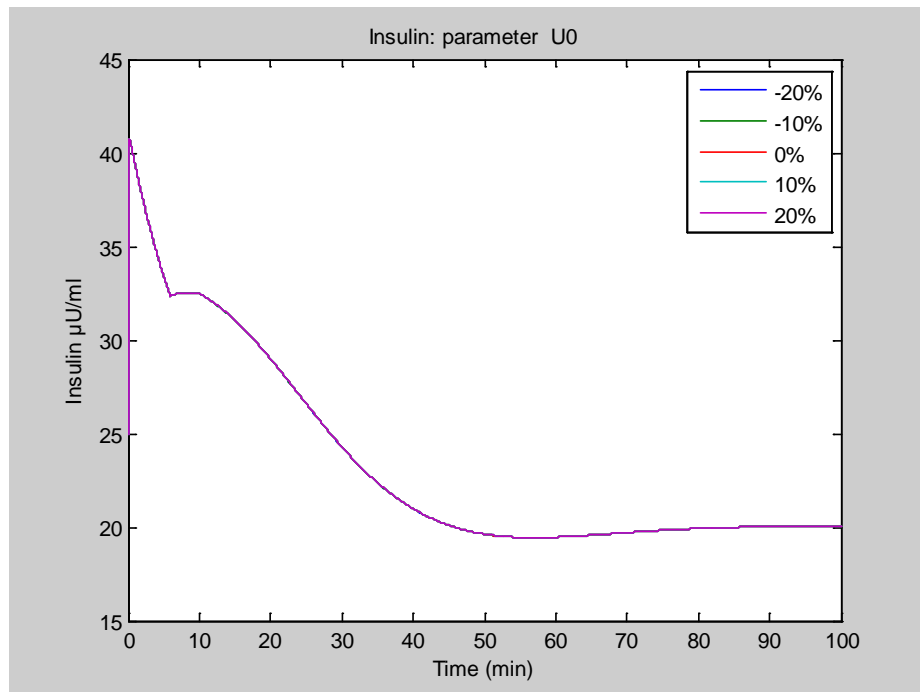


Figure 5.46: Insulin Response due to variation of parameter  $U_0$ .

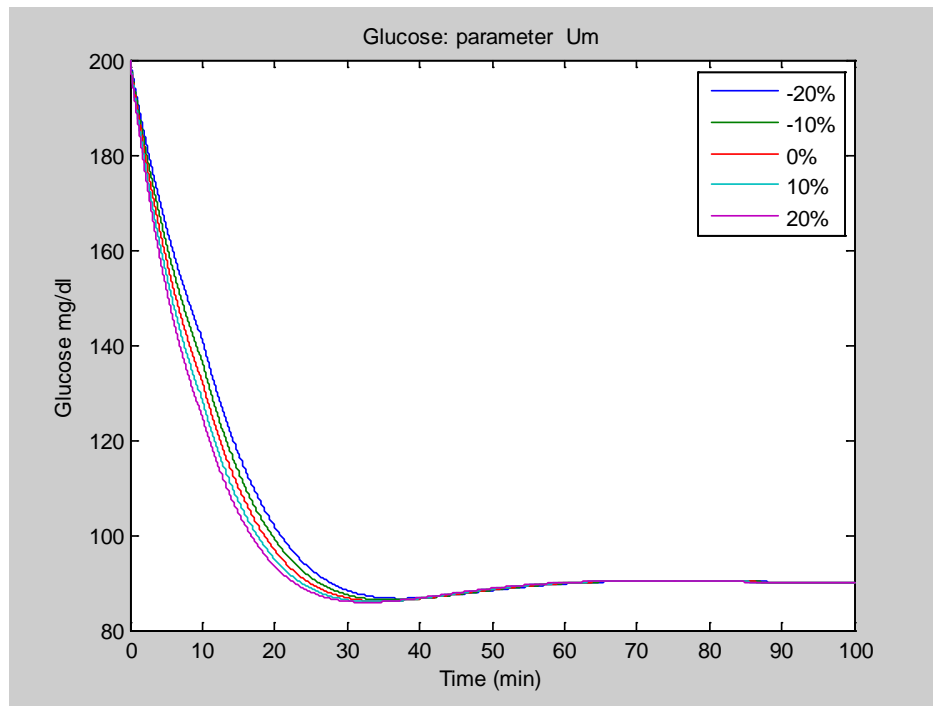
(10)  $U_m$ 

Figure 5.47: Glucose Response due to variation of parameter  $U_m$ .

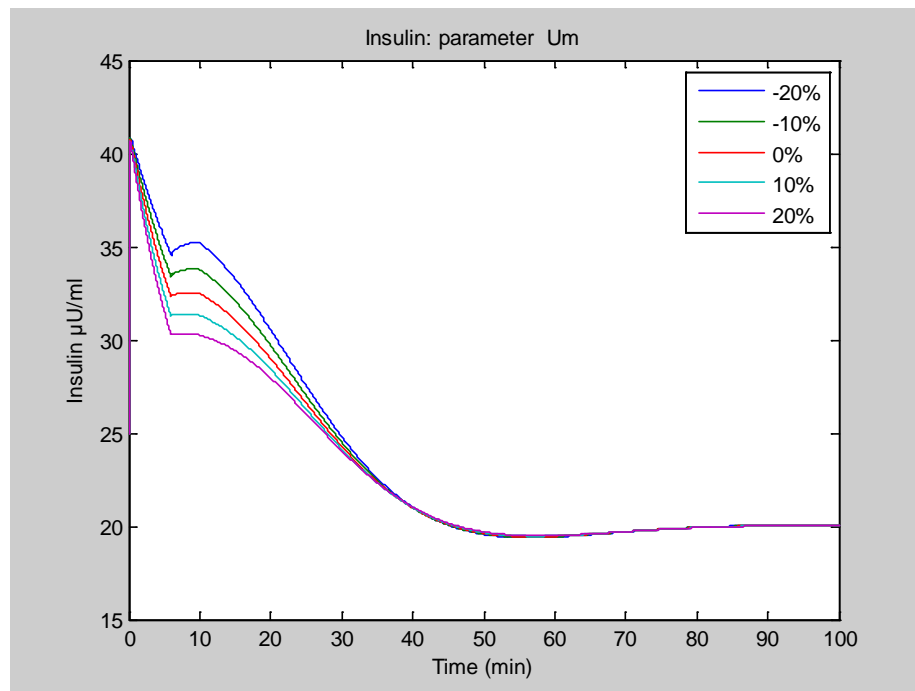


Figure 5.48: Insulin Response due to variation of parameter  $U_m$ .

(11) Beta:

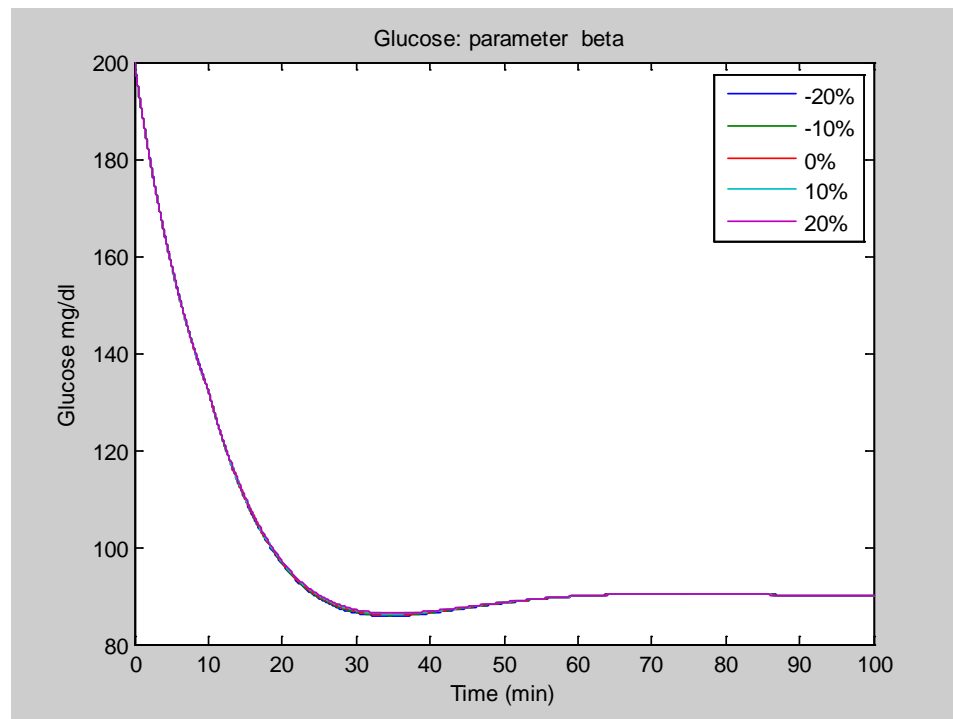


Figure 5.49: Glucose Response due to variation of parameter Beta.

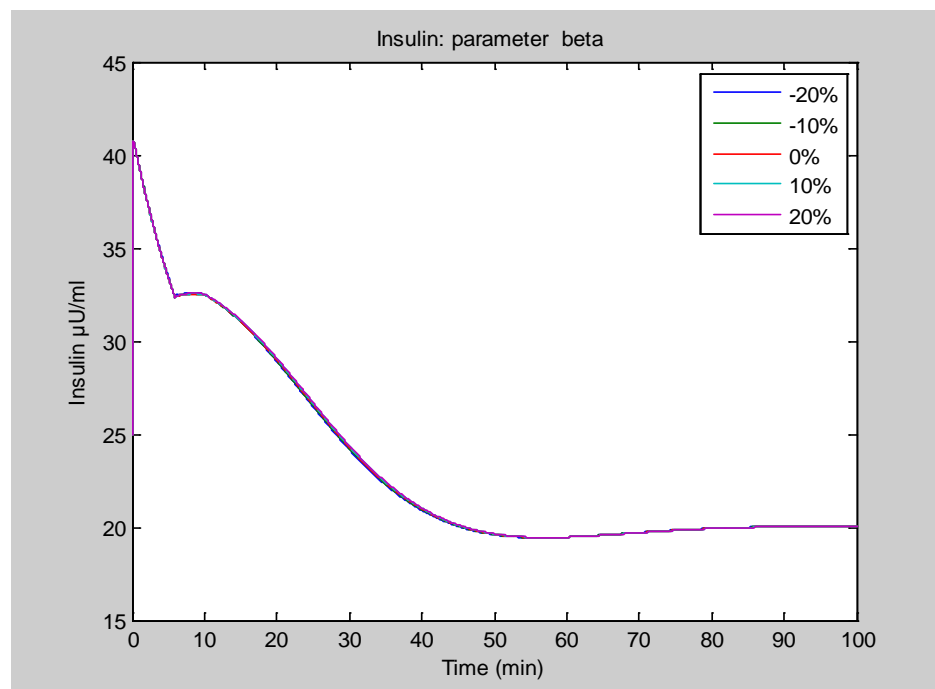


Figure 5.50: Insulin Response due to variation of parameter Beta.

(12) C4:

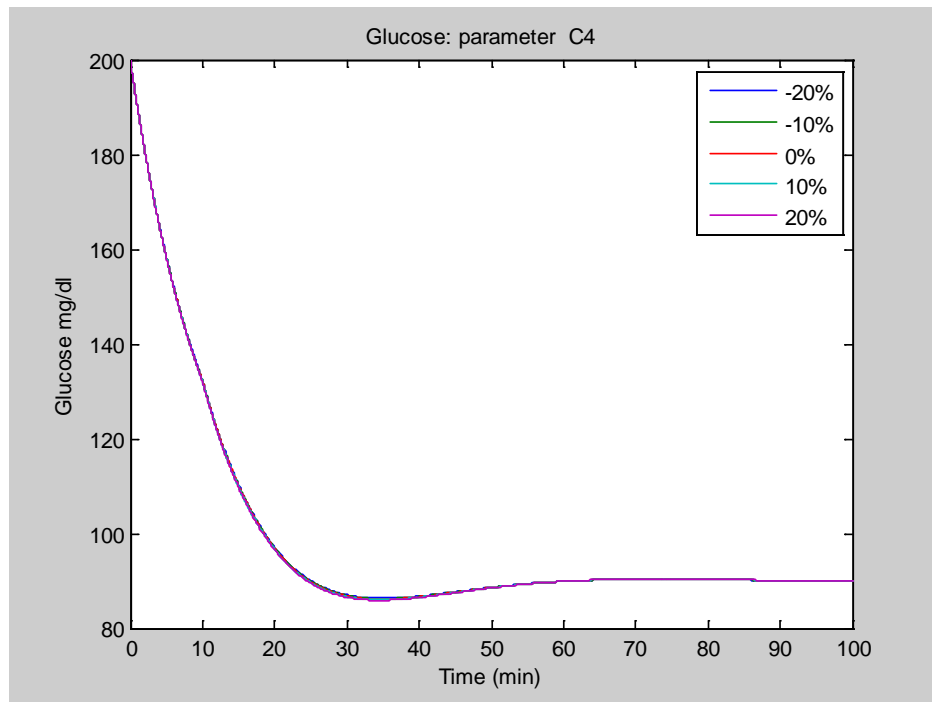


Figure 5.51: Glucose Response due to variation of parameter C4.

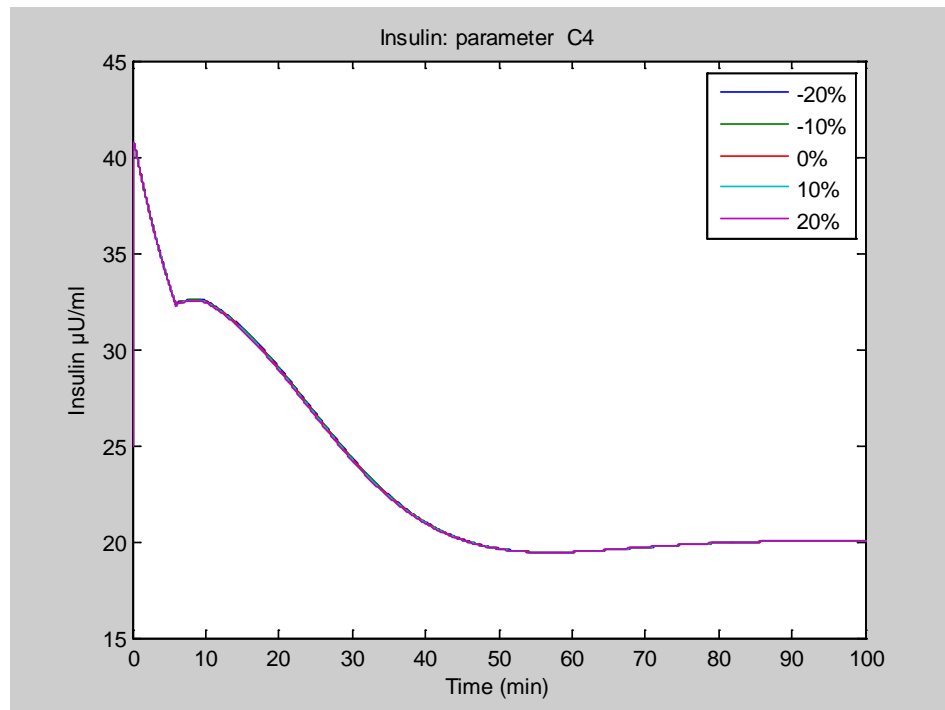
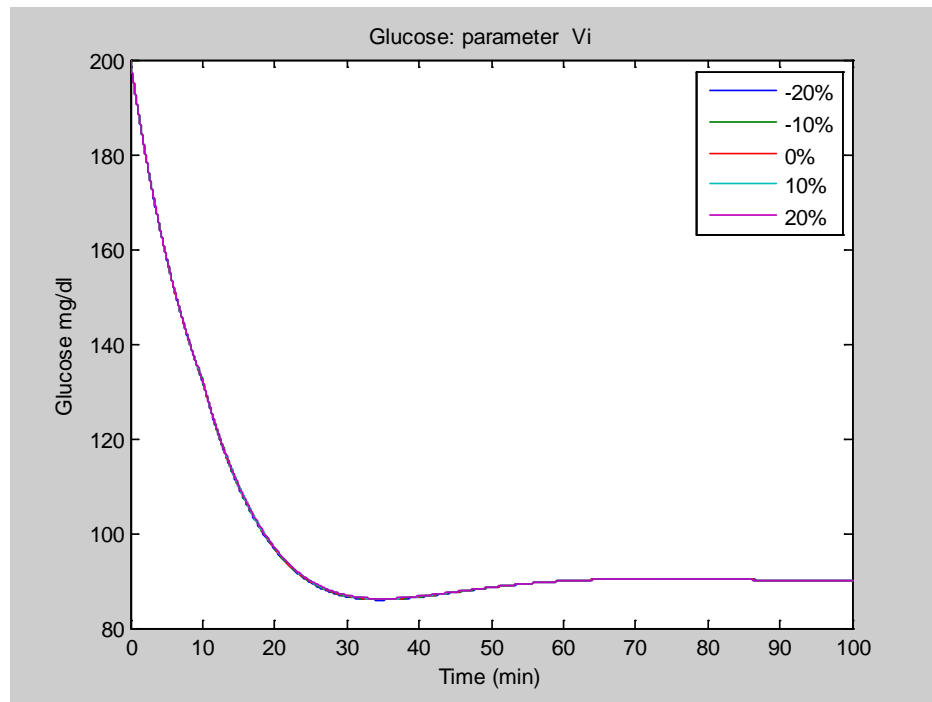
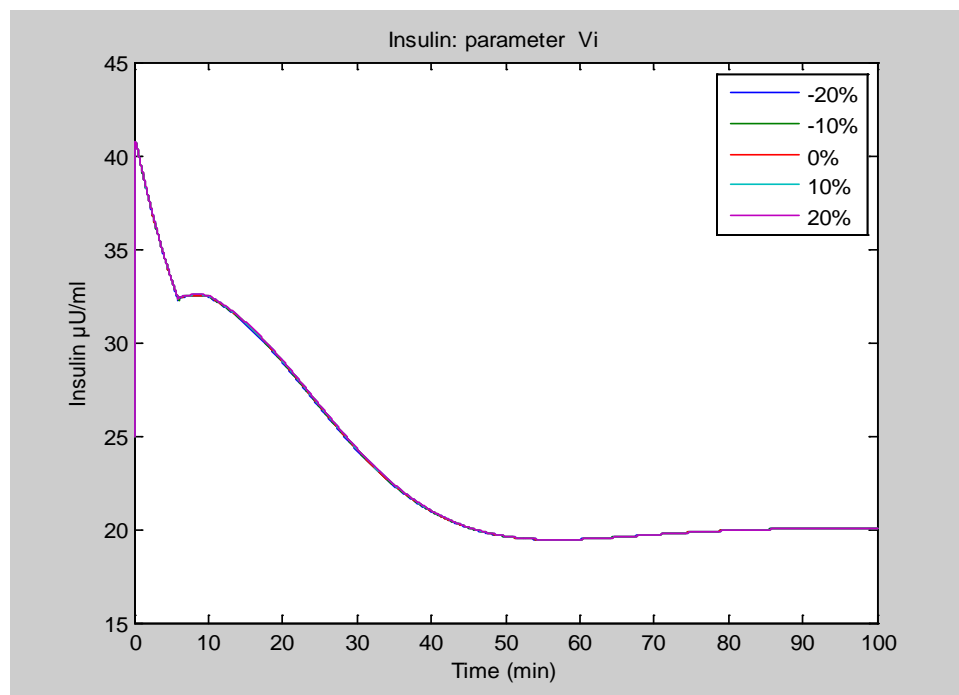


Figure 5.52: Insulin Response due to variation of parameter C4.

(13) Vi:



**Figure 5.53: Glucose Response due to variation of parameter Vi.**



**Figure 5.54: Insulin Response due to variation of parameter Vi.**

(15)  $t_i$ :

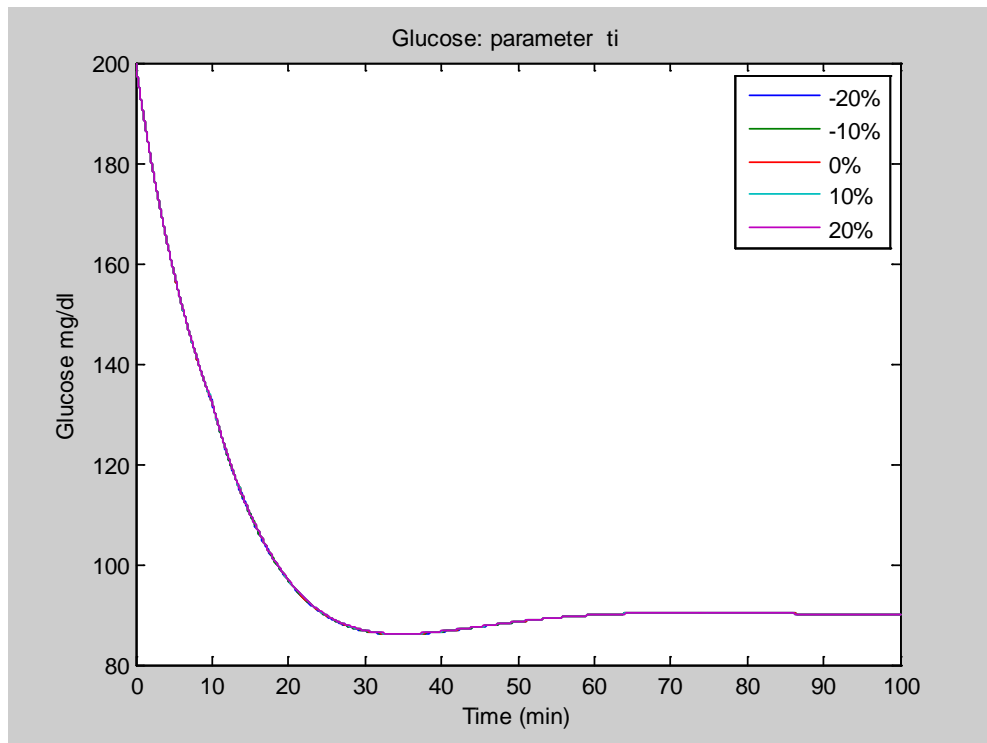


Figure 5.55: Glucose Response due to variation of parameter  $t_i$ .

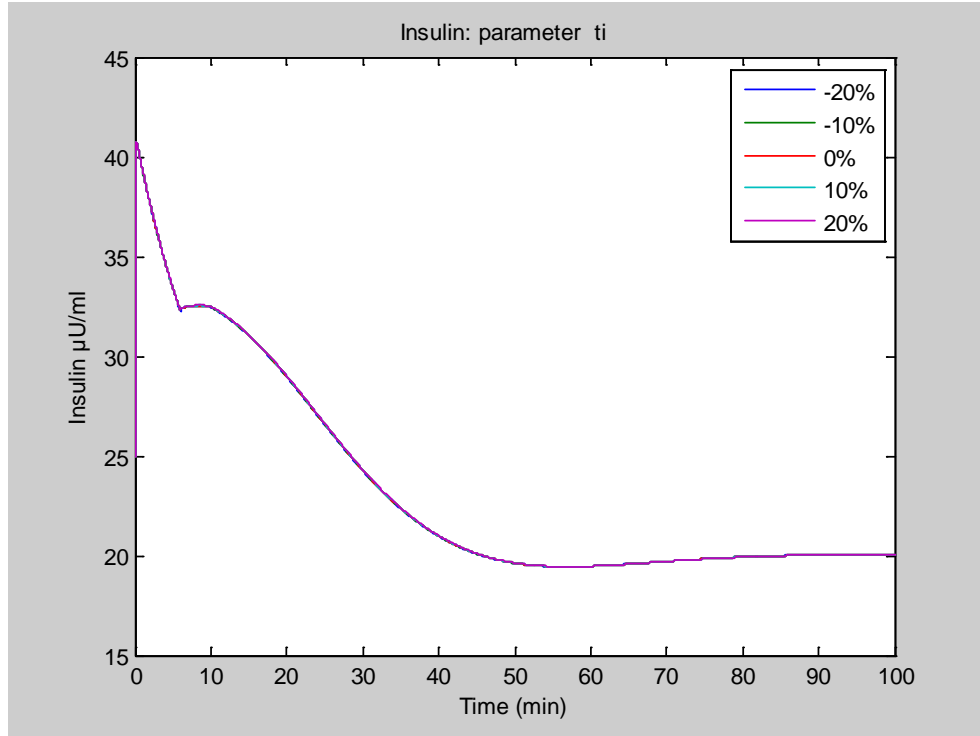


Figure 5.56: Insulin Response due to variation of parameter  $t_i$ .

(16) E:

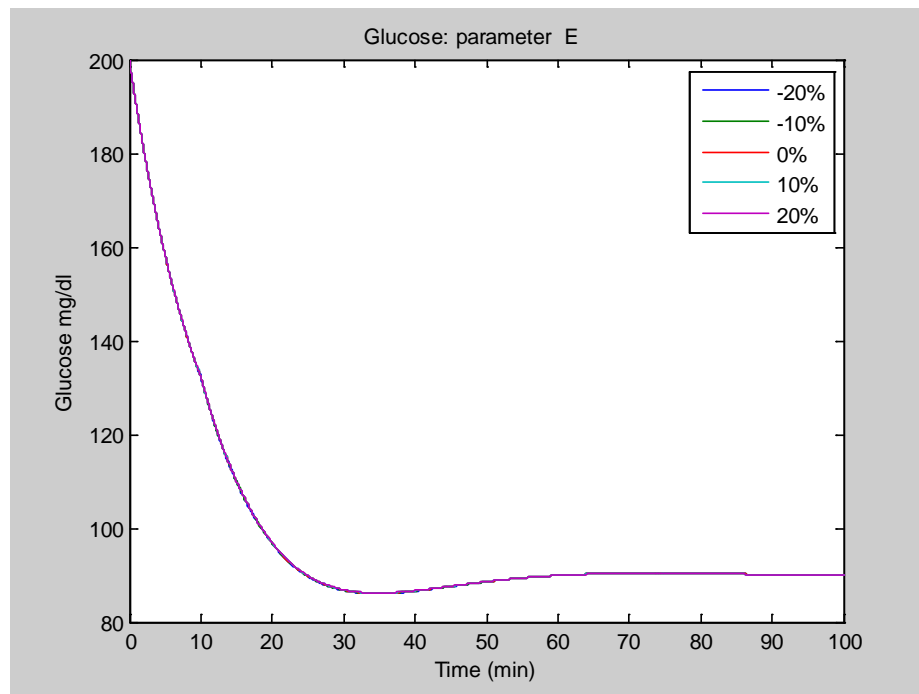


Figure 5.57: Glucose Response due to variation of parameter  $E$ .

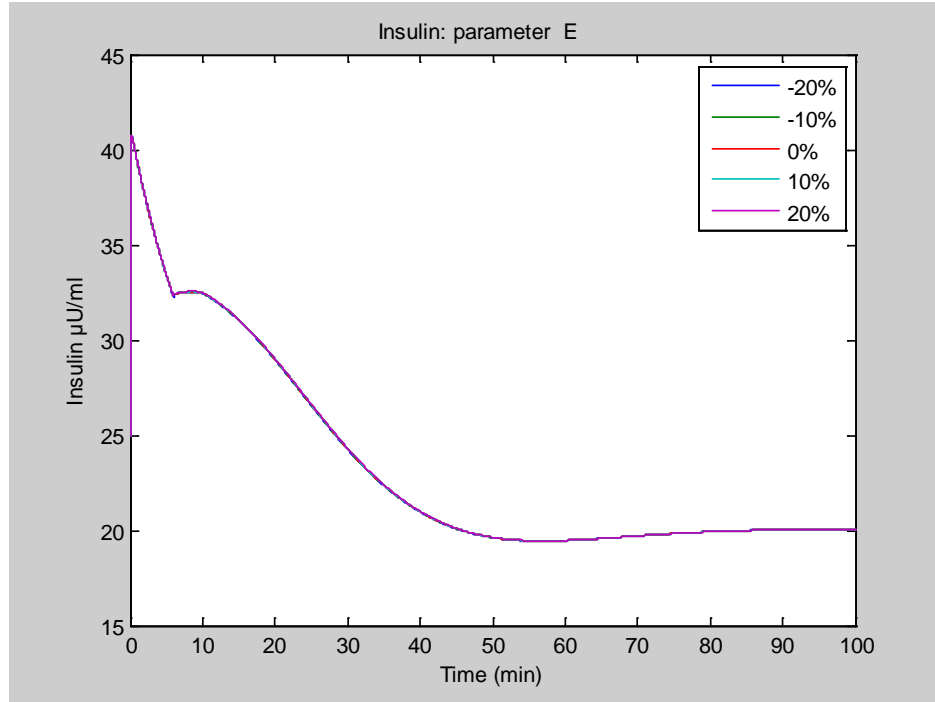


Figure 5.58: Insulin Response due to variation of parameter E.

(17)  $R_g$ :

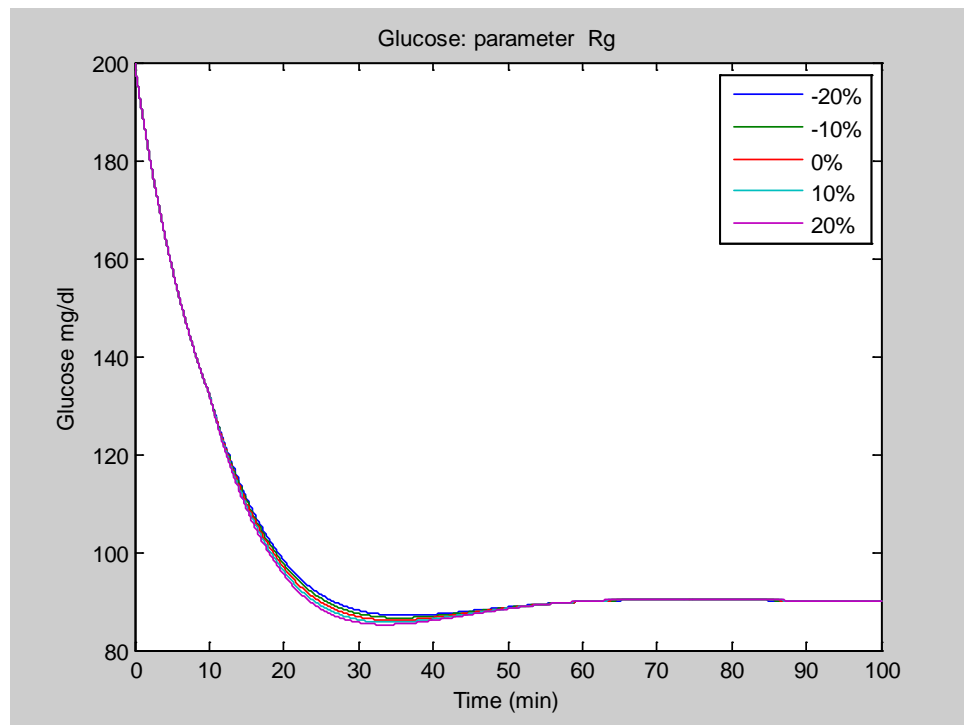


Figure 5.59: Glucose Response due to variation of parameter  $R_g$ .



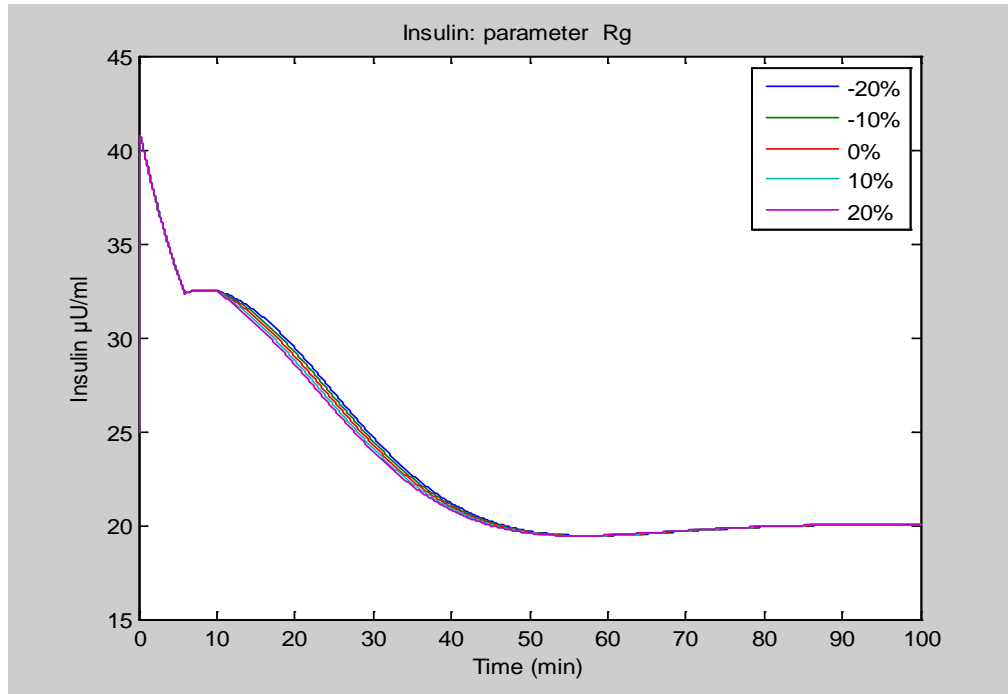


Figure 5.60: Insulin Response due to variation of parameter  $R_g$ .

(18) Alpha:

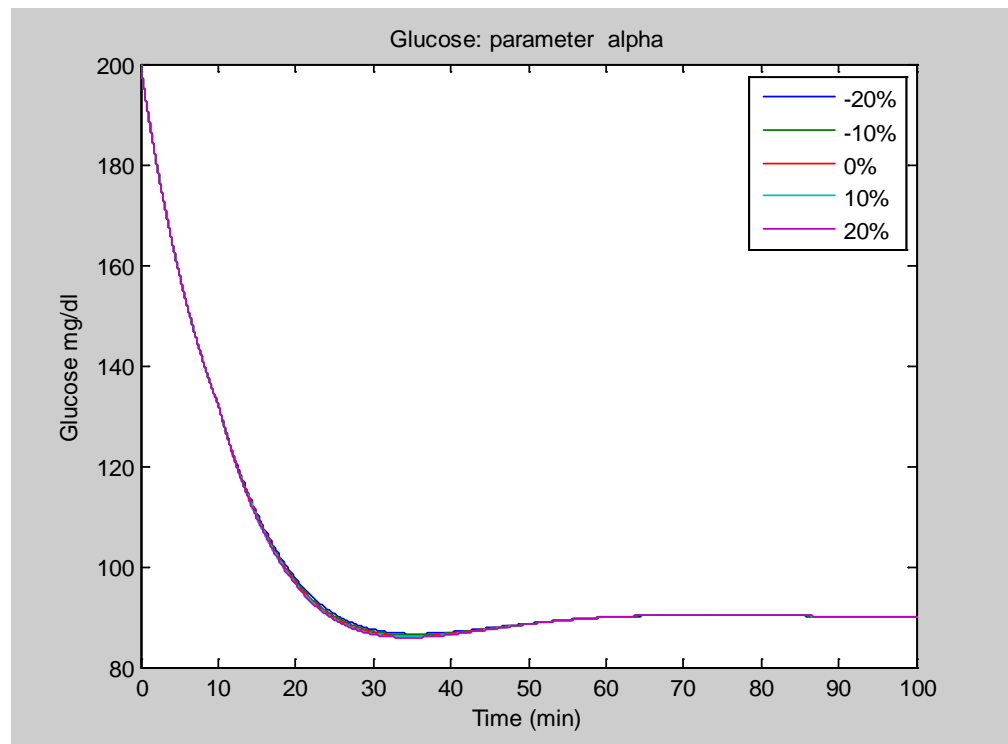


Figure 5.61: Glucose Response due to variation of parameter  $\alpha$ .

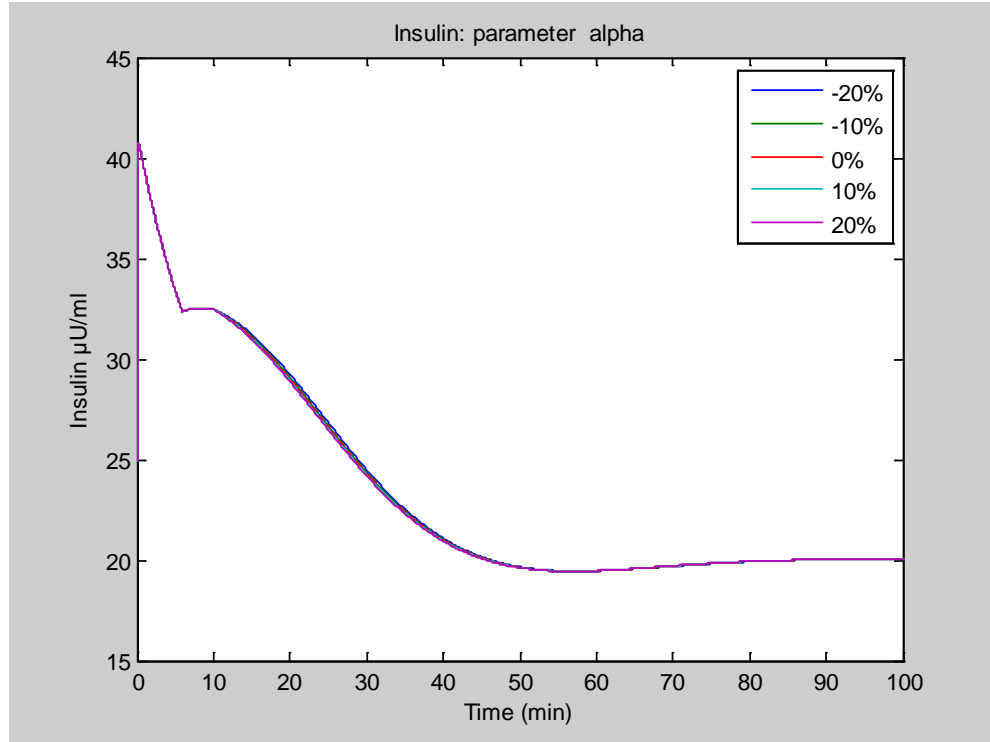


Figure 5.62: Insulin Response due to variation of parameter alpha.

(19)  $V_p$ :

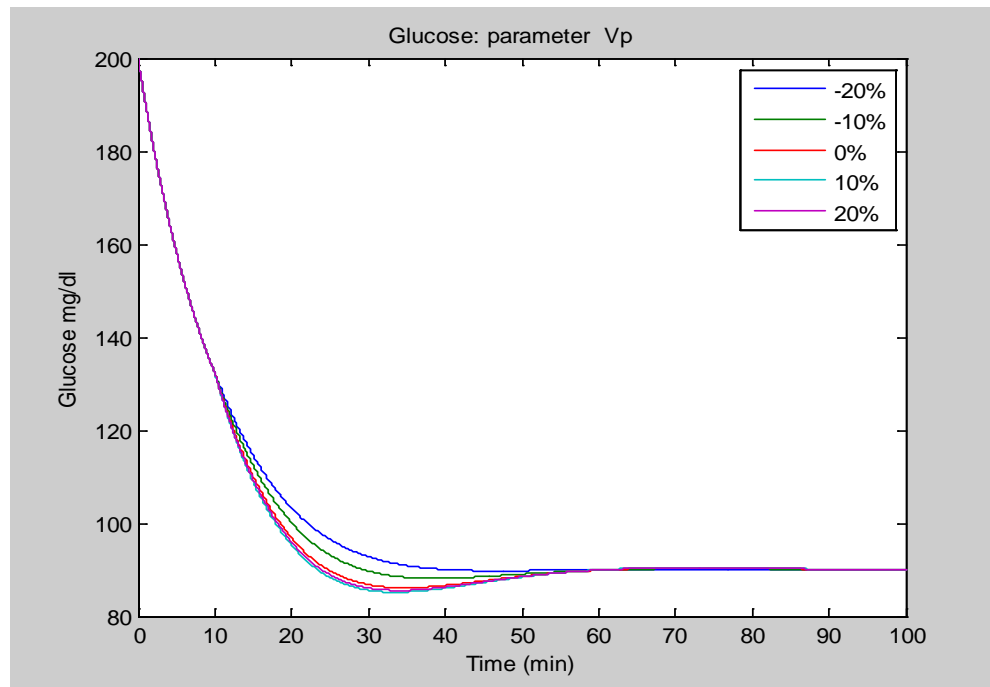


Figure 5.63: Glucose Response due to variation of parameter  $V_p$ .

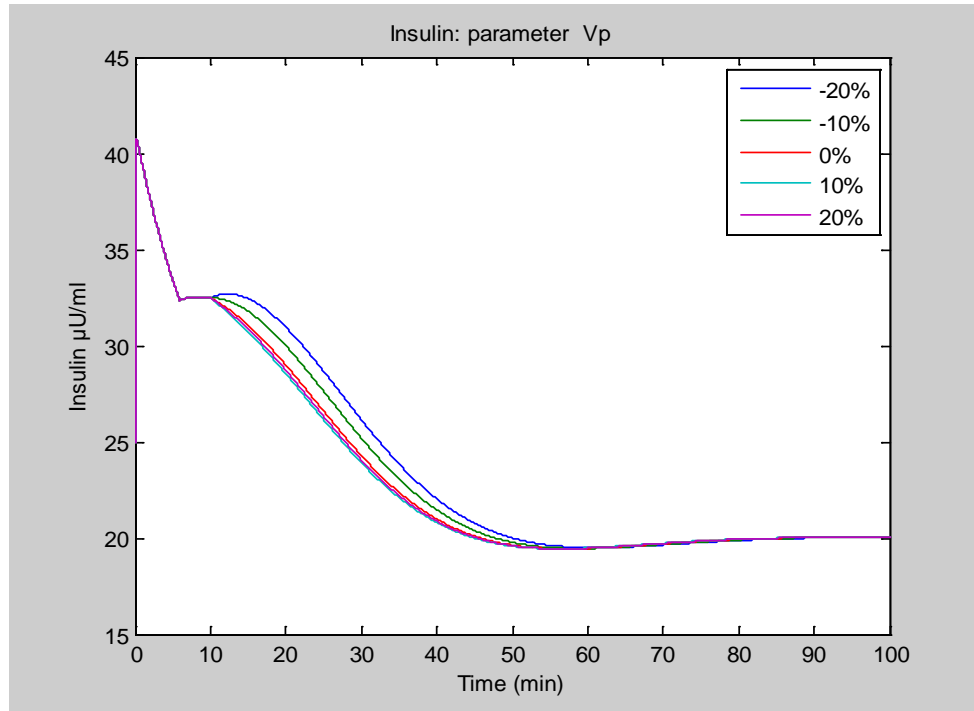


Figure 5.64: Insulin Response due to variation of parameter  $V_p$ .

(20) C5:

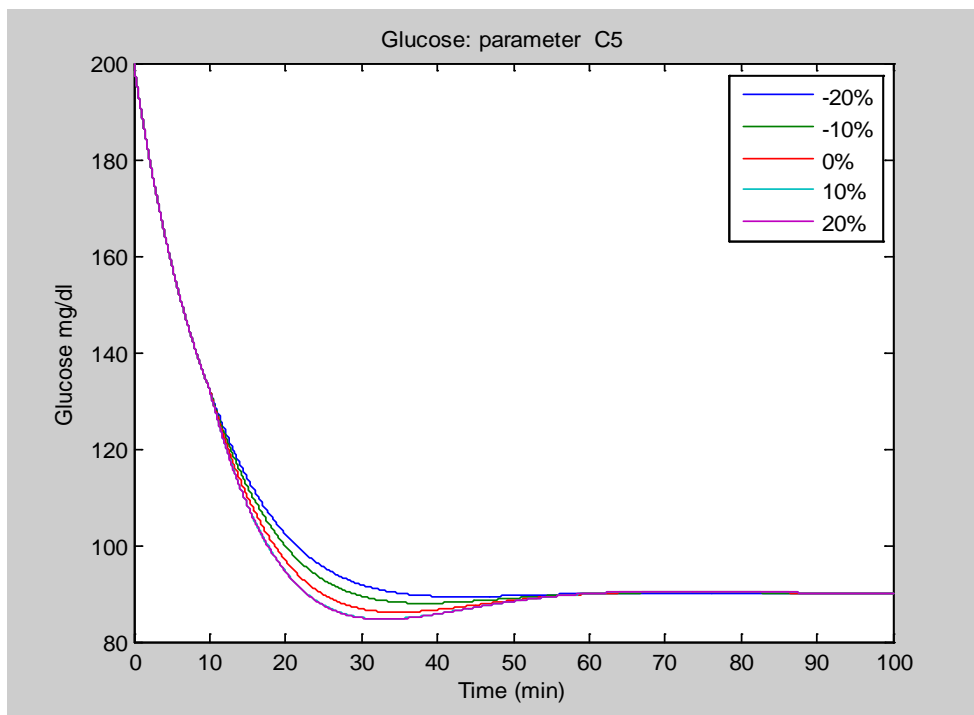
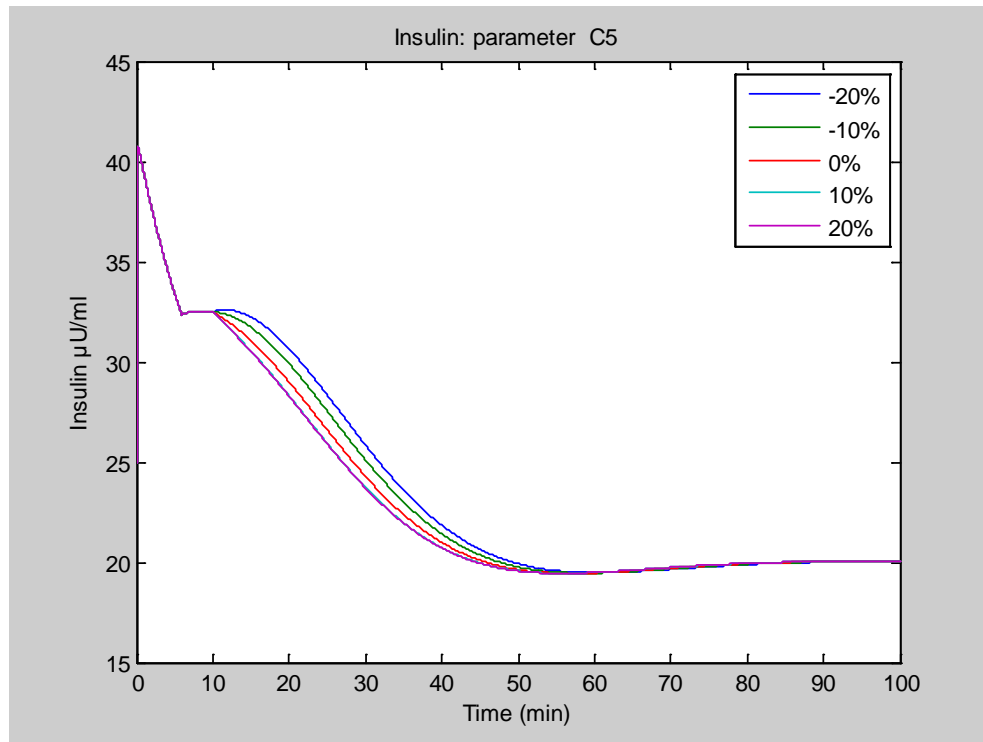


Figure 5.65: Glucose Response due to variation of parameter  $C_5$ .



**Figure 5.66: Insulin Response due to variation of parameter C5.**

Changing the parameter of the system by  $\pm 20\%$  does not affect the performance of the system for most of the model parameters. Five parameters show notable effects. These parameters are:

$C5$  ,  $C3$  ,  $Vp$ ,  $Vg$ ,  $Rg$  ,  $Um$

#### **Medical explanation of this variation:**

1)  $Rg$ ,  $C5$ ,  $Vp$  are parameters of  $f_5$  which represent the hepatic glucose production. Changing these parameters affects the process of converting the stored sugar and fat to glucose which are then sent to the blood which, in turn, affects glucose concentration in the blood.

2)  $Um$ ,  $C3$  &  $Vg$  are parameters of  $f_3$  &  $f_4$ . The nonlinear term  $f_3 * f_4$  represents the relation of insulin-dependent glucose utilization by muscle, fat cells and other parts of the

body. So, the variation of these parameters has a direct effect on the glucose concentration.

For both cases, as glucose concentration varies due to parameter variations, the insulin concentration also varies in the same direction to compensate for these variations.

Despite parameter variations, the system is still stable and it reaches the steady-state value in the normal range.

## **5.2. Nonlinear Simulation Validation**

In the last section we tested our design by using a linearized model which showed interesting results. However, the real situation is represented by the nonlinear model. So, we need to use the nonlinear model in simulation, instead of the linearized one, to verify our design and to show its applicability to the treatment of diabetes patients.

### **5.2.1. State Feedback (Closed Loop)**

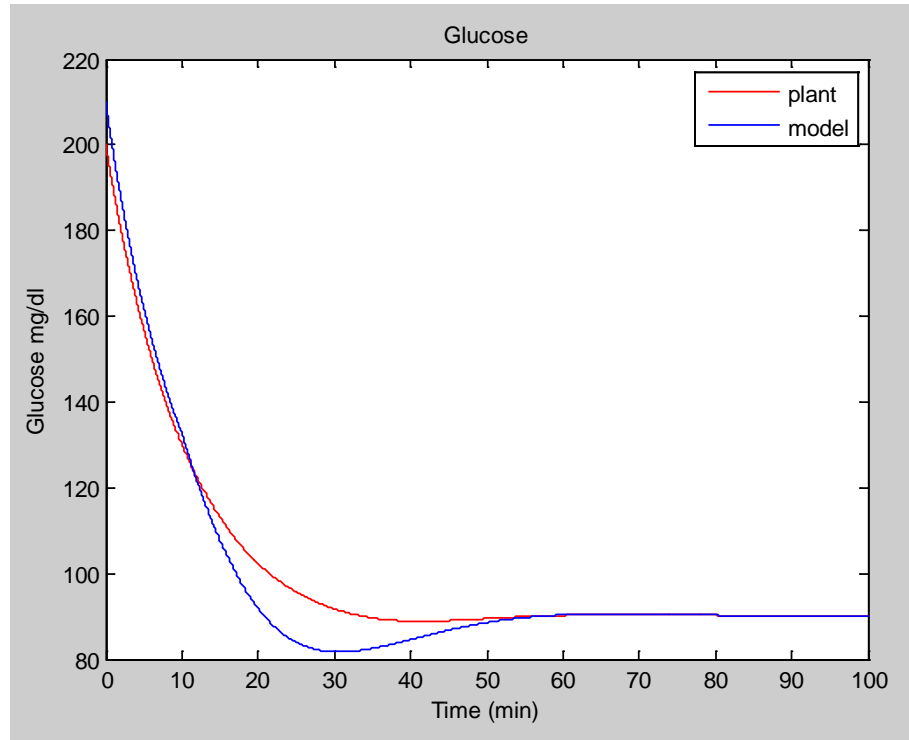


Figure 5.67: Glucose Response (closed loop).

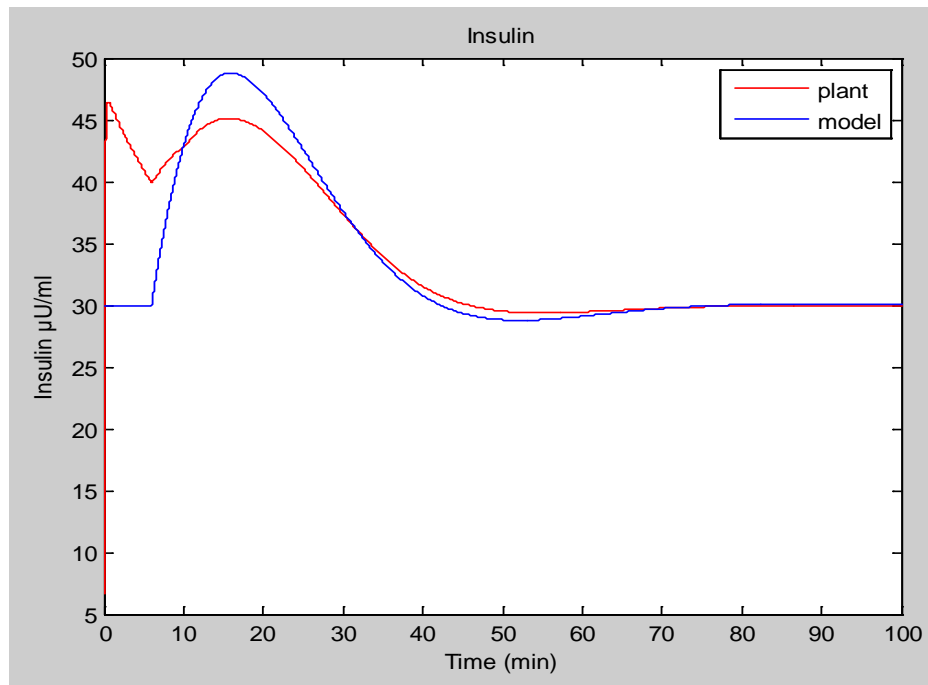


Figure 5.68: Insulin Response (State Feedback).

### 5.2.3. Time Delay Analysis:

(A) Maximum Time Delay Testing:

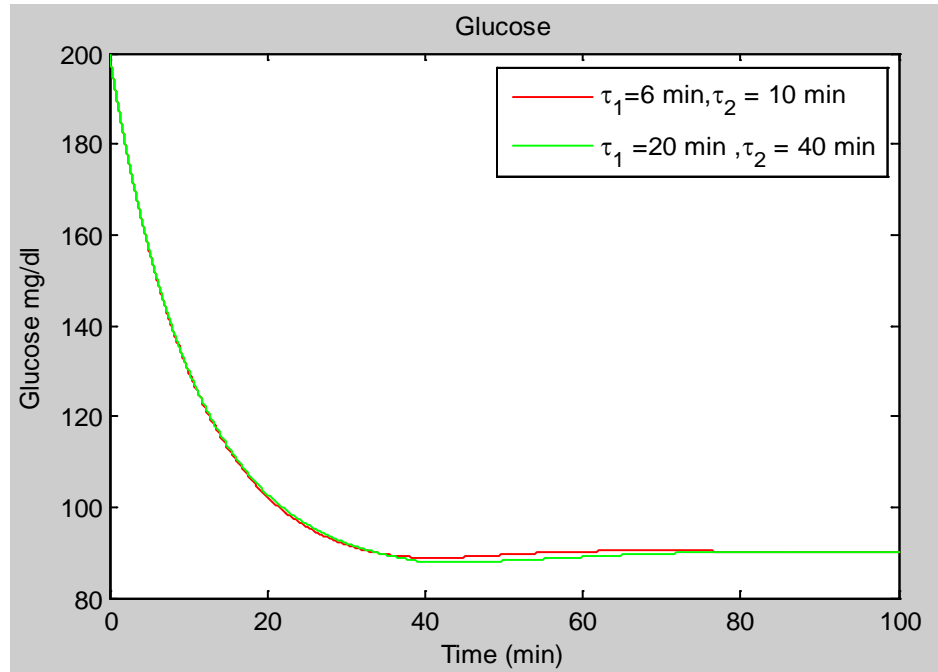


Figure 5.69: Glucose Response (max time delay).

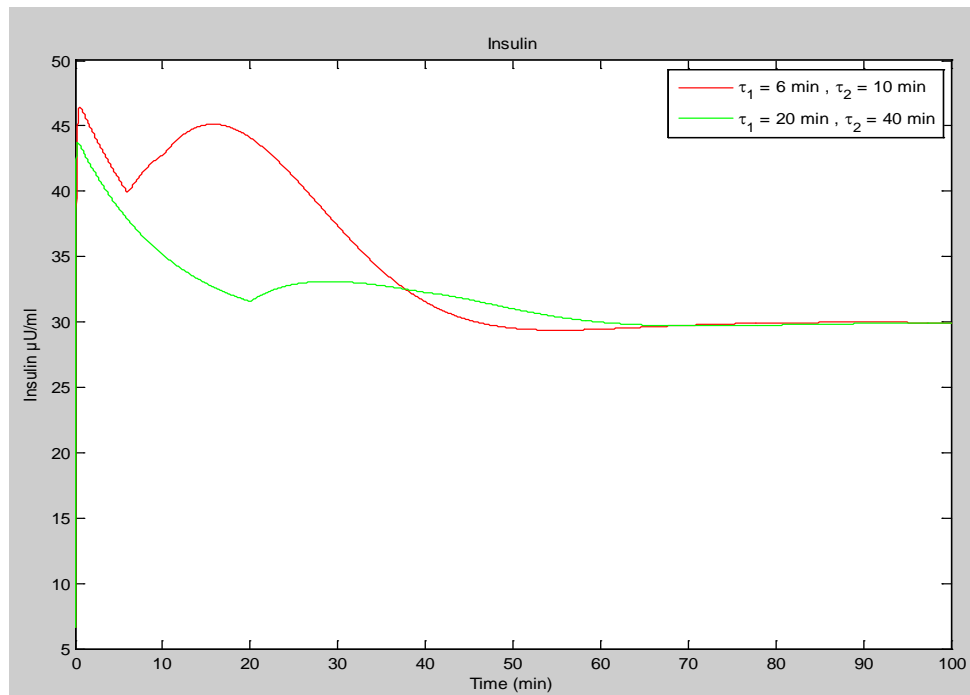
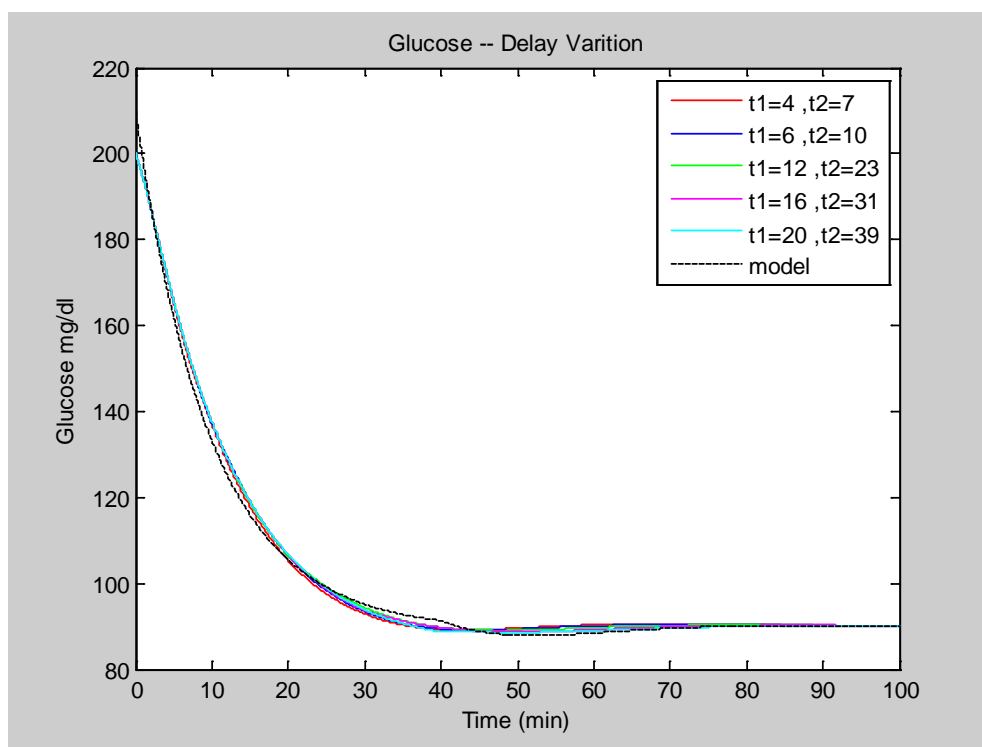


Figure 5.70: Insulin Response (max time delay).

B) Time delay Variations (Robustness Analysis):



**Figure 5.71: Glucose Response for time delay variations.**



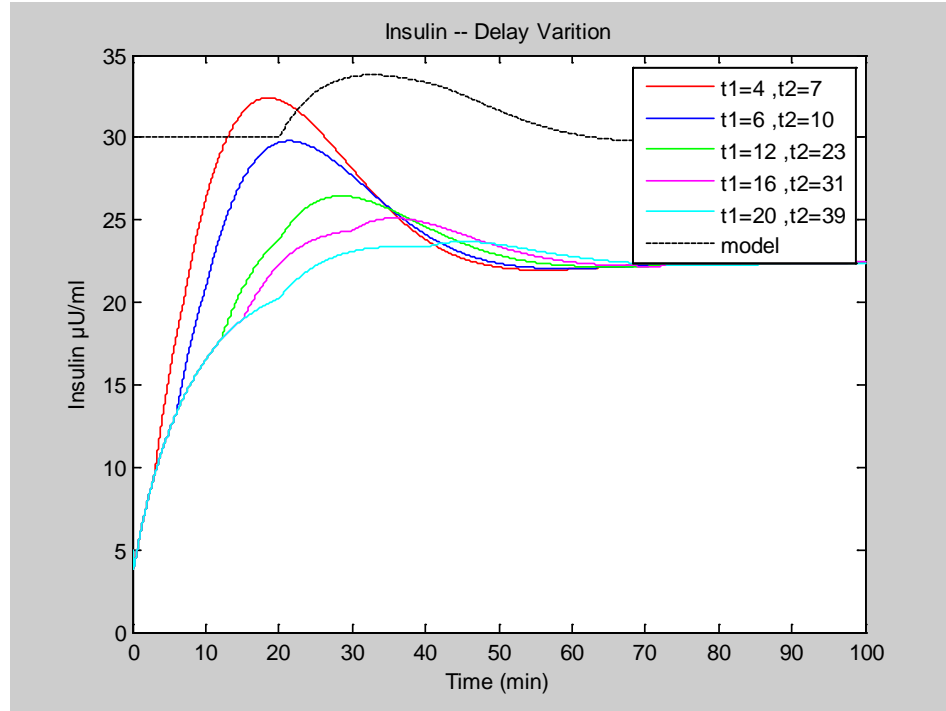


Figure 5.72: Insulin Response for time delay variations.

### 5.2.3. Model Mismatch:

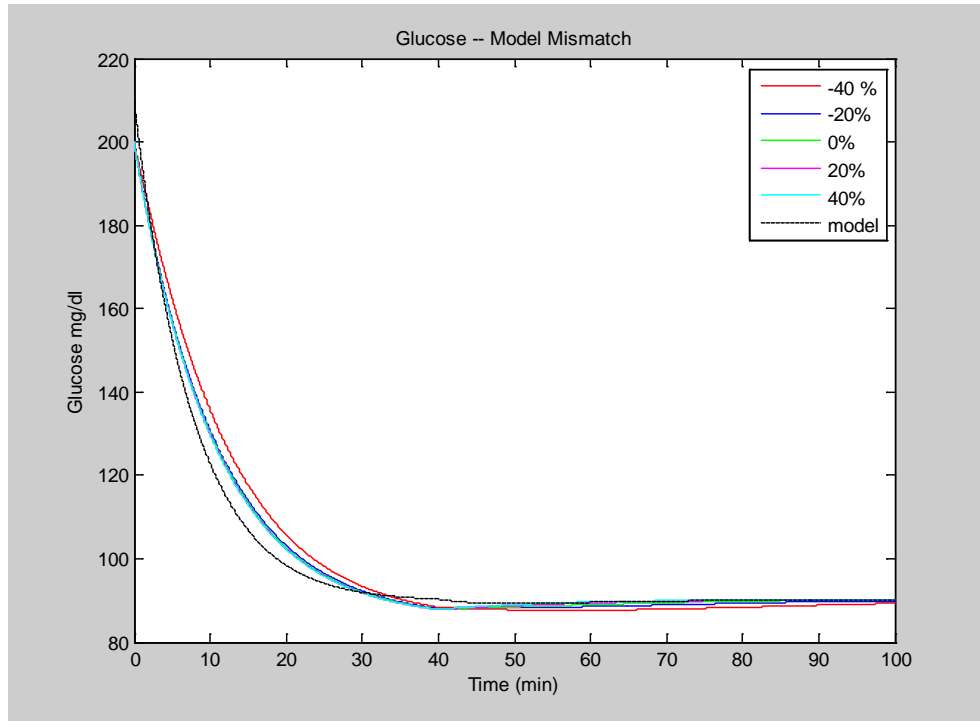


Figure 5.73: Glucose Response for model mismatch.

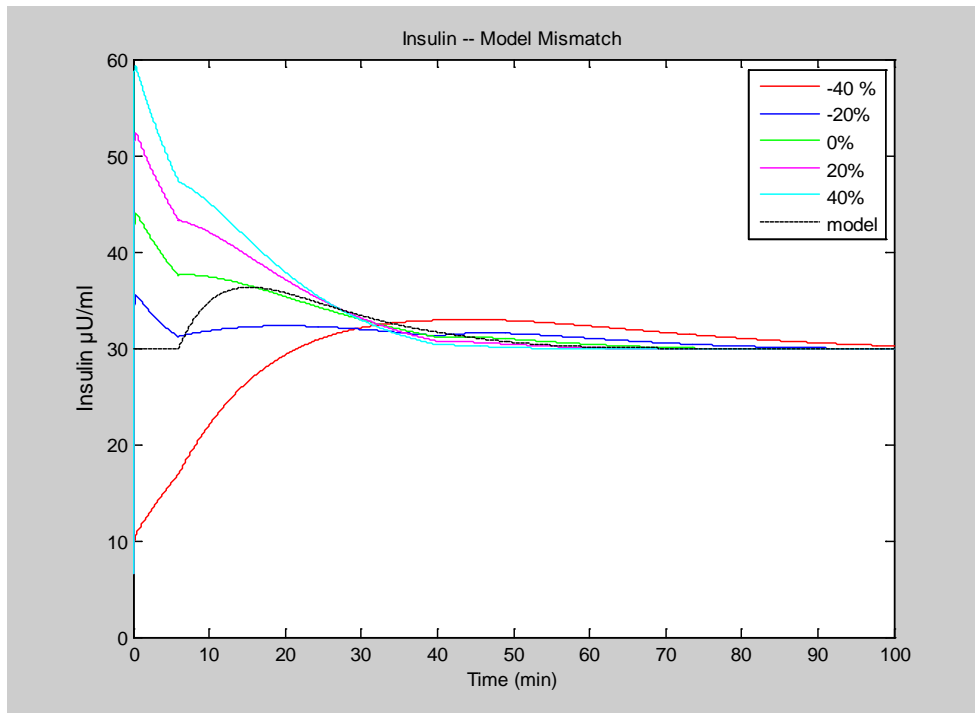


Figure 5.74: Insulin Response for model mismatch.

#### 5.2.4. Disturbance Analysis:

In this section we will test our design due to various glucose dosage (meals) and we will compare it to the linear model results.

(a) 100 mg

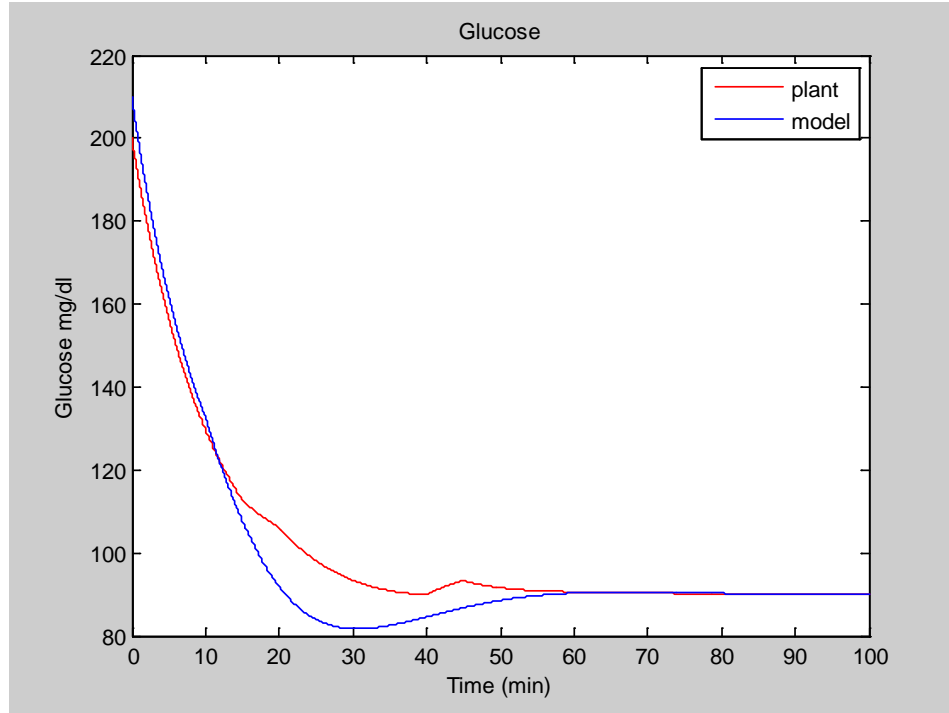


Figure 5.75: Glucose Response with 100 mg meal disturbance.

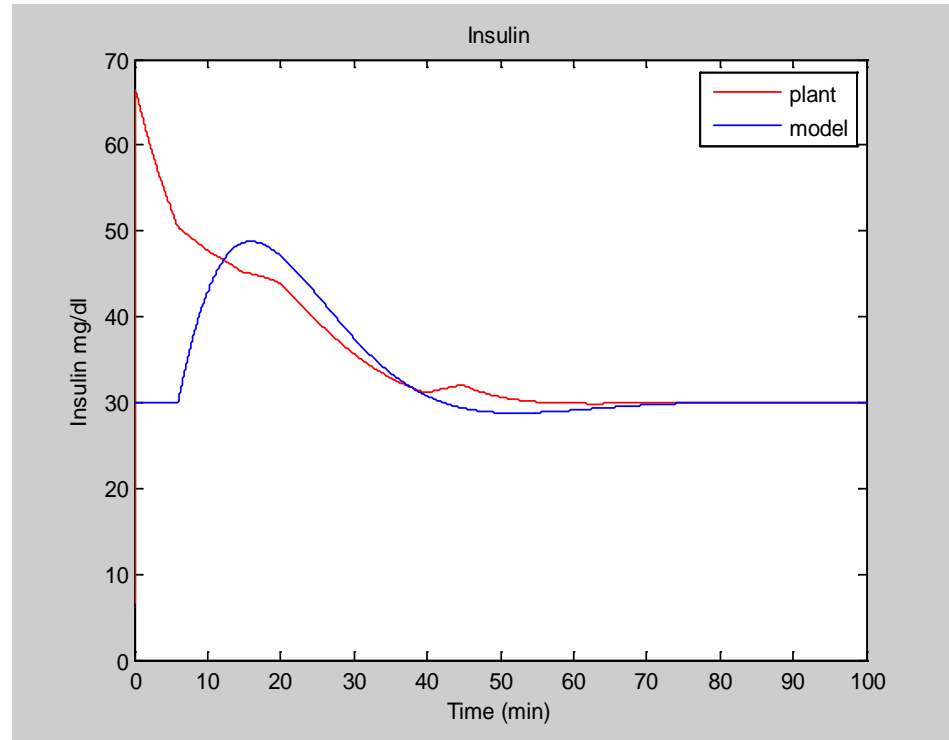


Figure 5.76: Insulin Response with 100 mg meal disturbance.

(b) 200 mg:

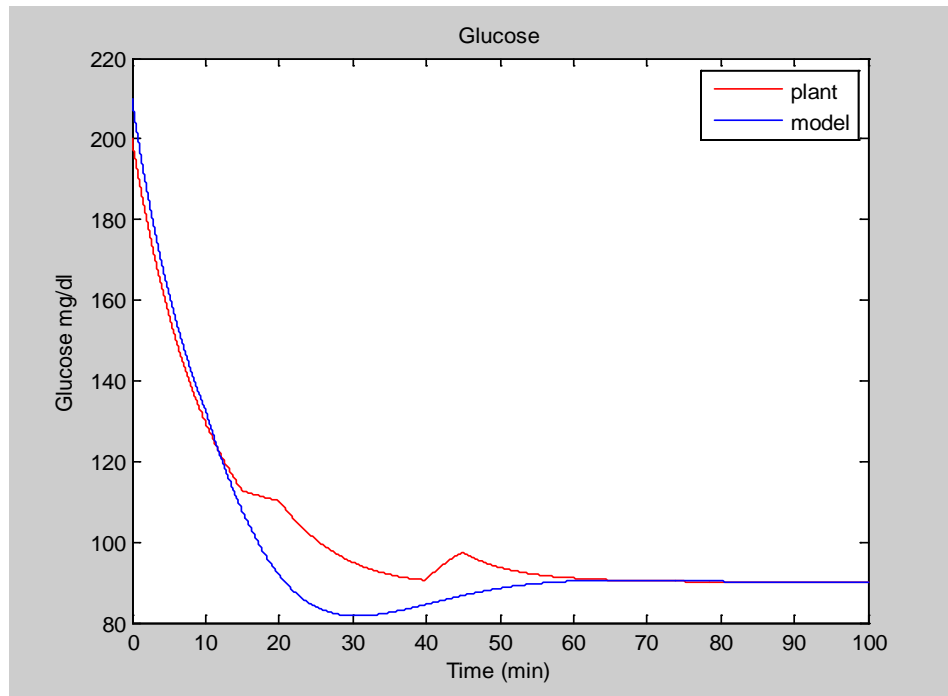


Figure 5.77: Glucose Response with 200 mg meal disturbance.

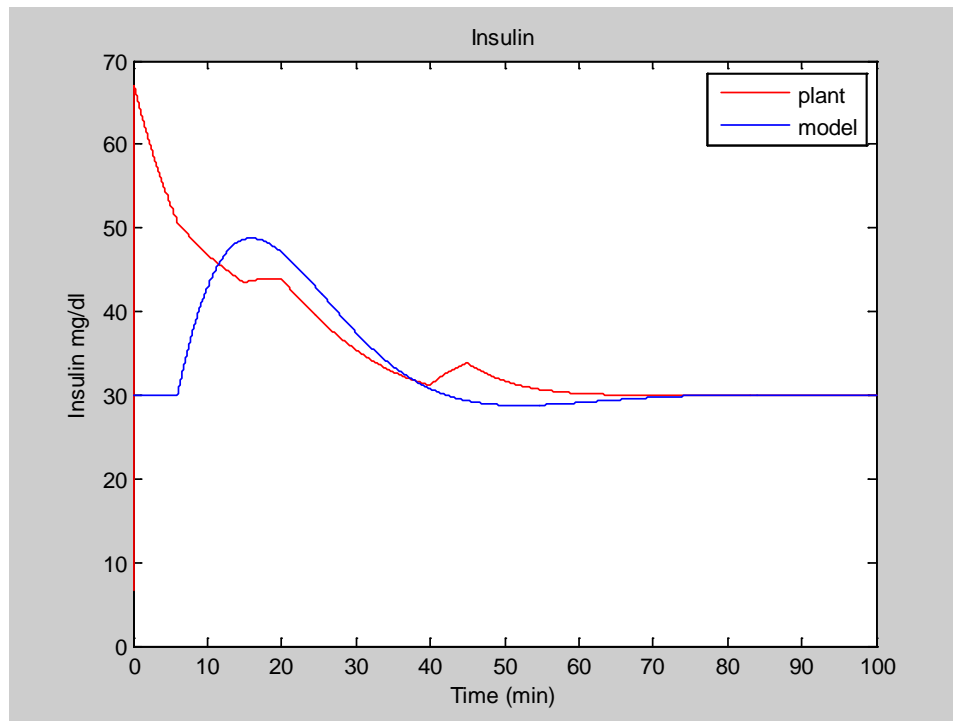
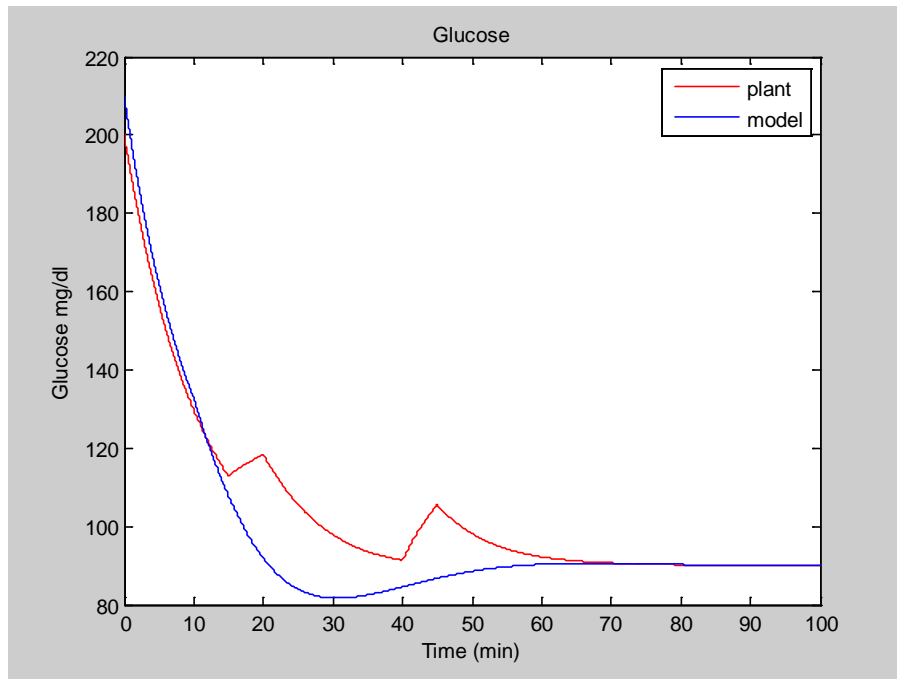
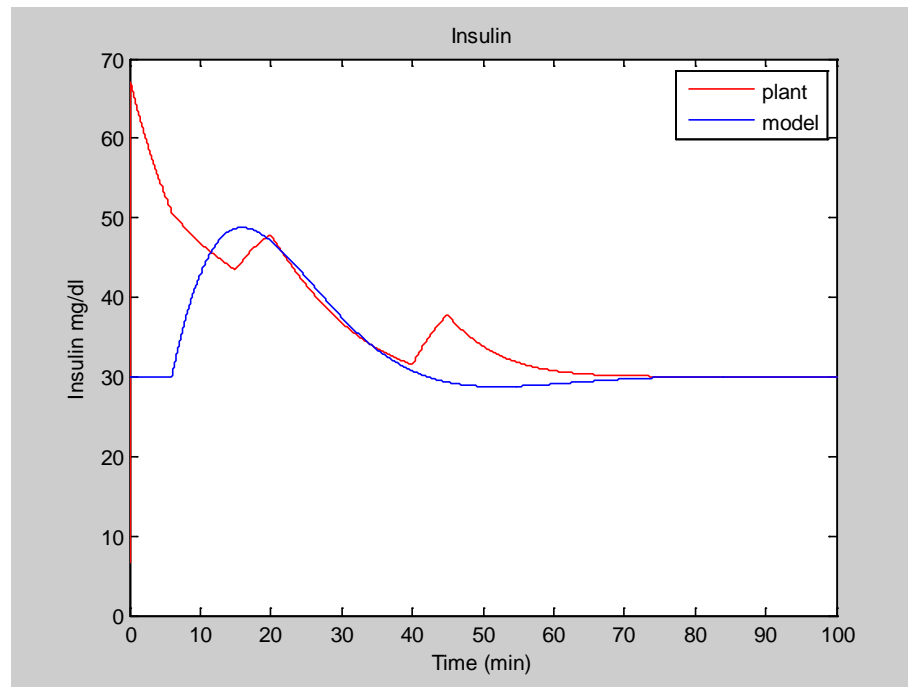


Figure 5.78: Insulin Response with 200 mg meal disturbance.

(2) 400 mg:



**Figure 5.79: Glucose Response with 400 mg meal disturbance.**



**Figure 5.80: Insulin Response with 400 mg meal disturbance.**

(e) 800 mg:

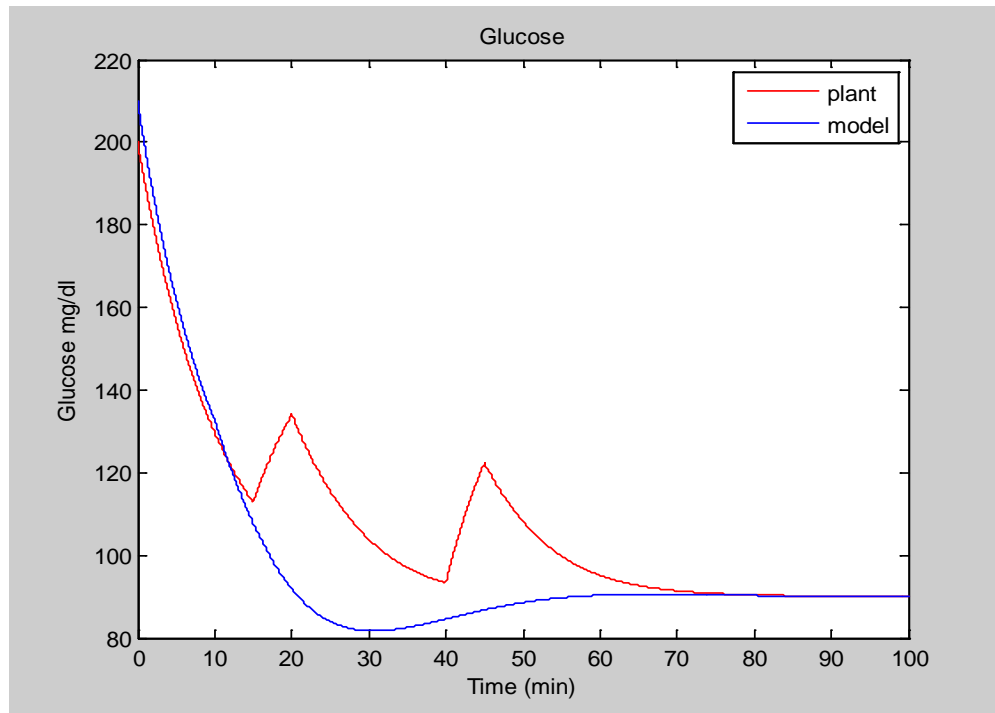


Figure 5.81: Glucose Response with 800 mg meal disturbance.

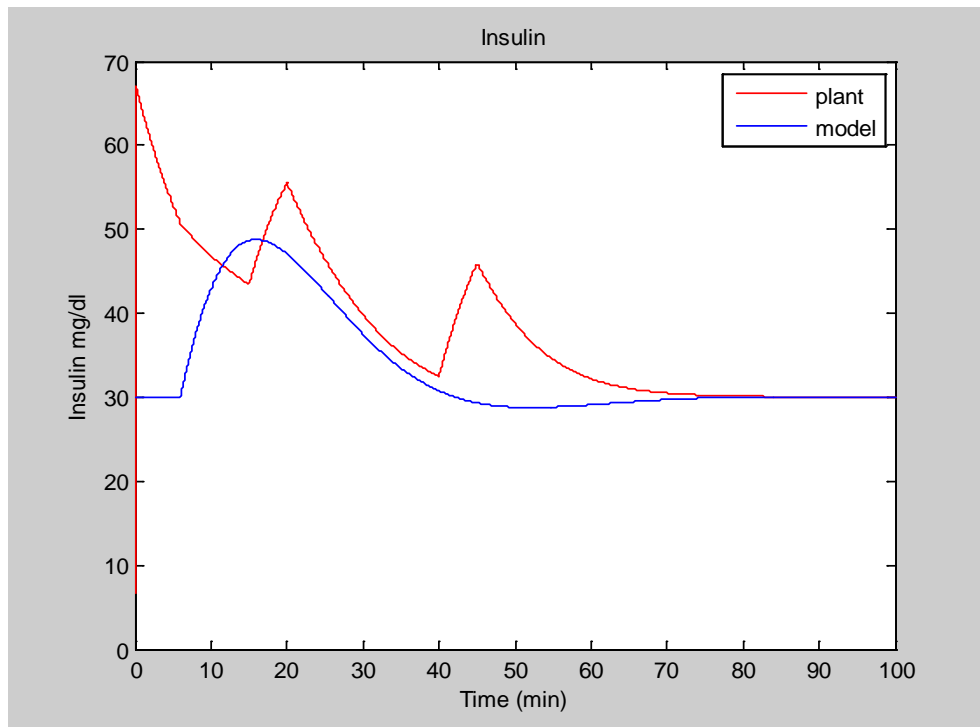


Figure 5.82: Insulin Response with 800 mg meal disturbance.

f) 1000 mg:

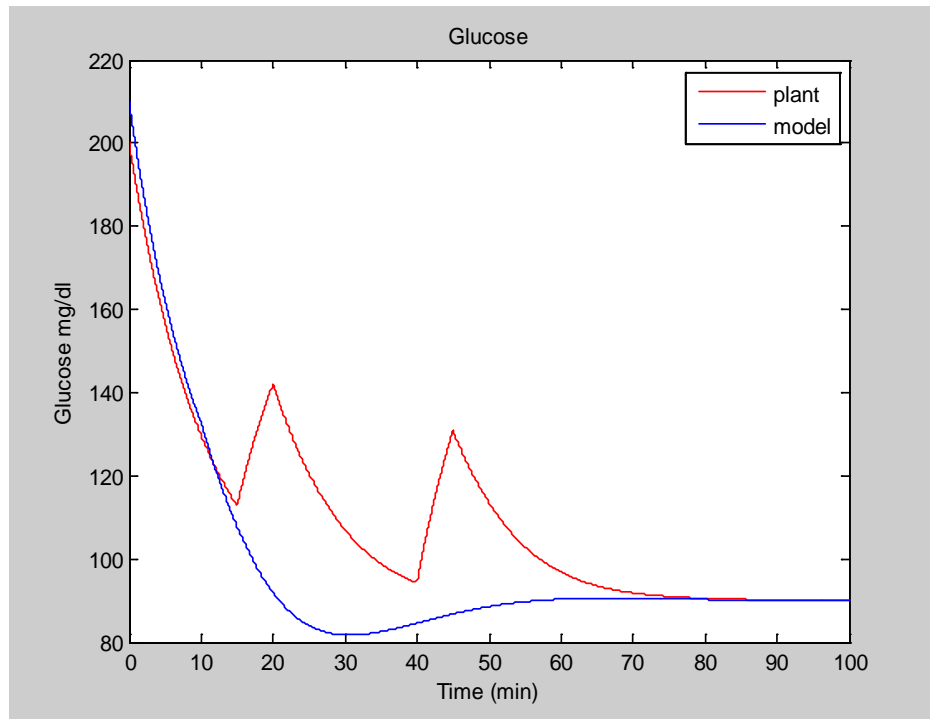


Figure 5.83: Glucose Response with 1000 mg meal disturbance.

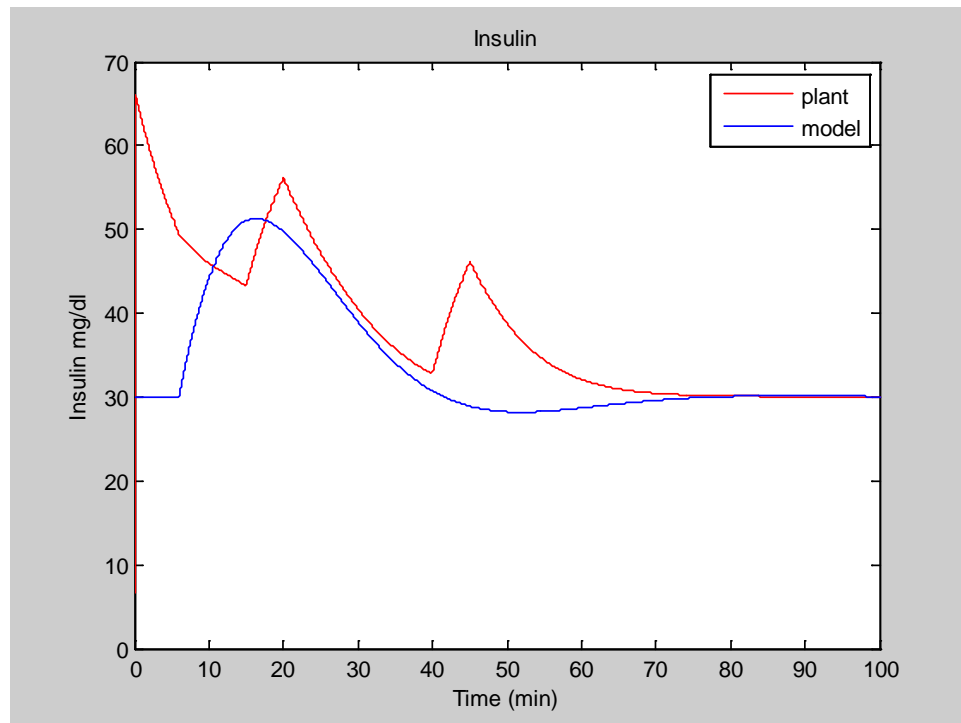
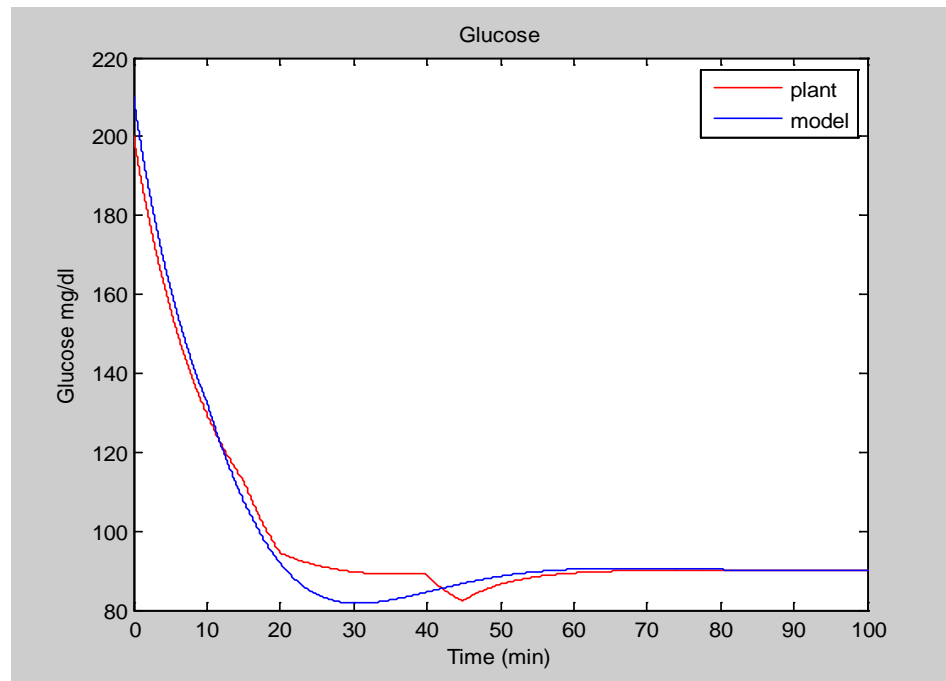


Figure 5.84: Insulin Response with 1000 mg meal disturbance.

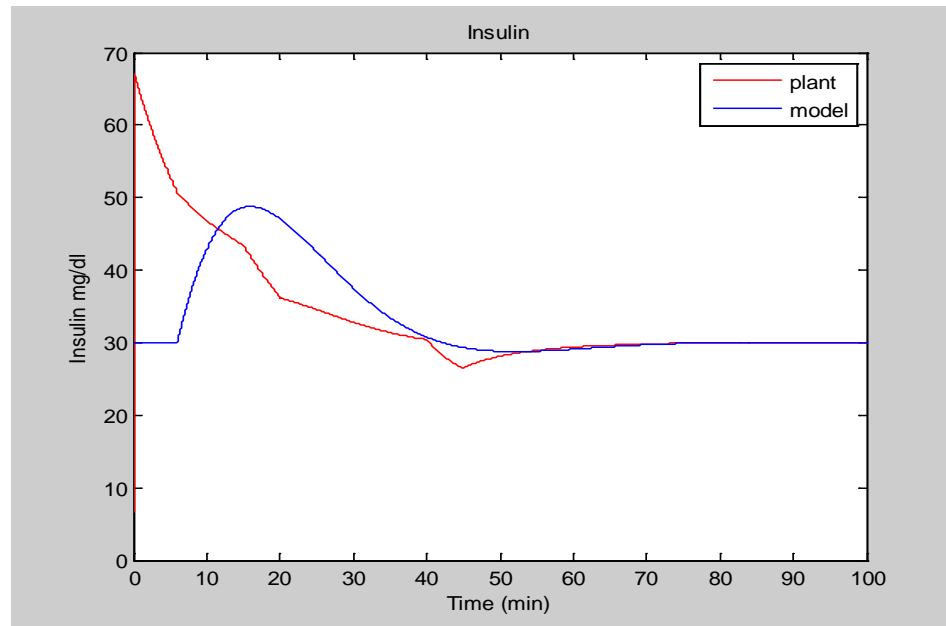


We can notice from previous simulation that the maximum amount of meal which our design can handle is about 1000 mg per sample which in our case ( $1000 * 500 = 500$  g) while in the linear case the maximum limit is 800 g. in fact, this is a good result from medical point of view because it is also an extreme case and it is rarely happen.

**b) Negative disturbance:**



**Figure 5.85: Glucose Response with negative meal disturbance of 200 mg.**



**Figure 5.86: Insulin Response with negative meal disturbance of 200 mg.**

### 5.2.5. Parameter variations:

In this section, we will test the parameter which shows a significant or notable effect in linearized model analysis.

(a) C3:

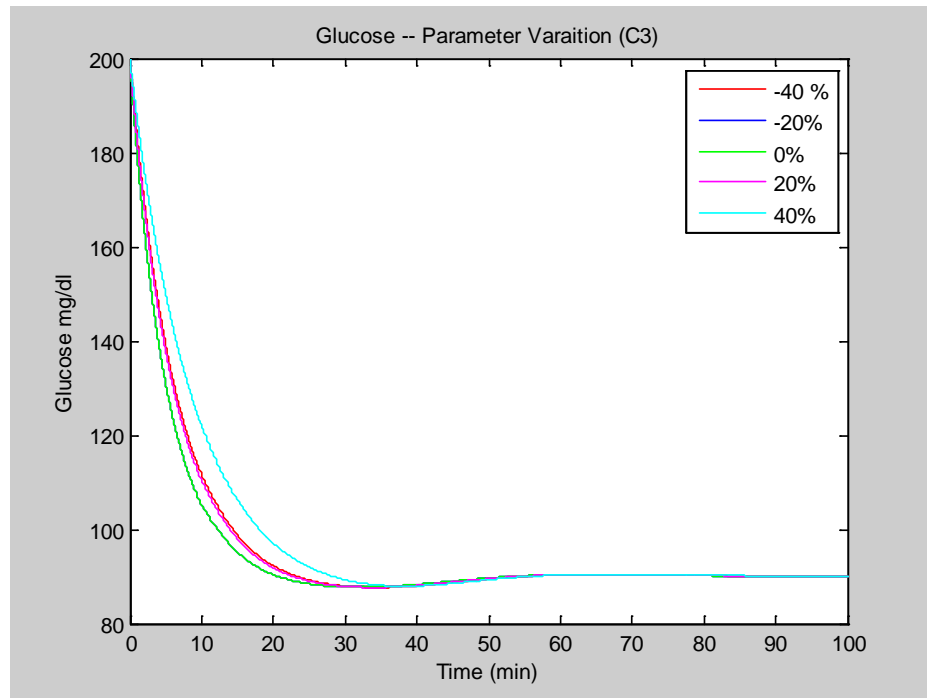


Figure 5.87: Glucose Response due to variation of parameter C3.

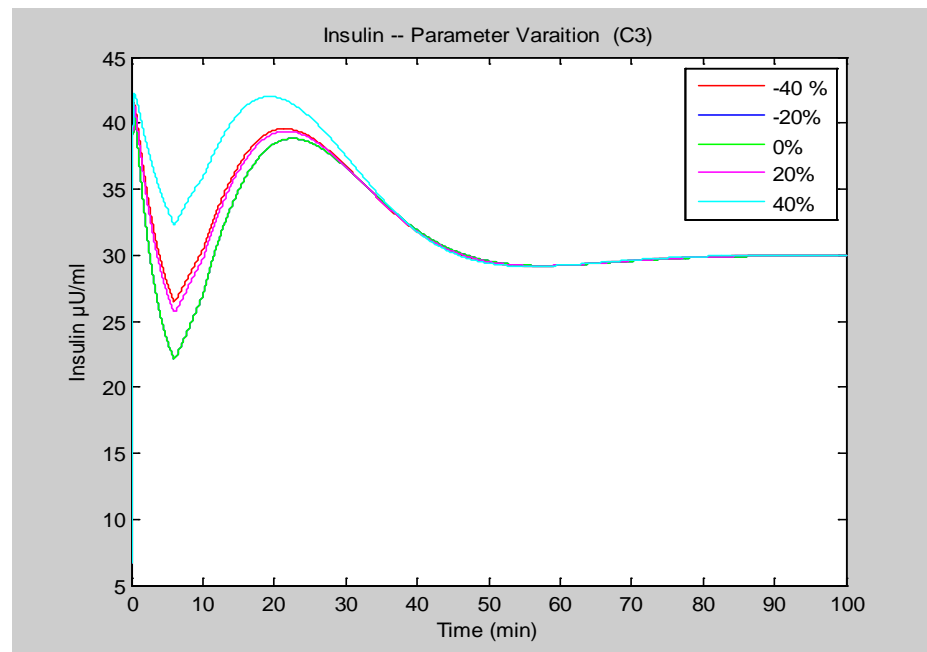


Figure 5.88: Insulin Response due to variations of parameter C3.

(b) C5:

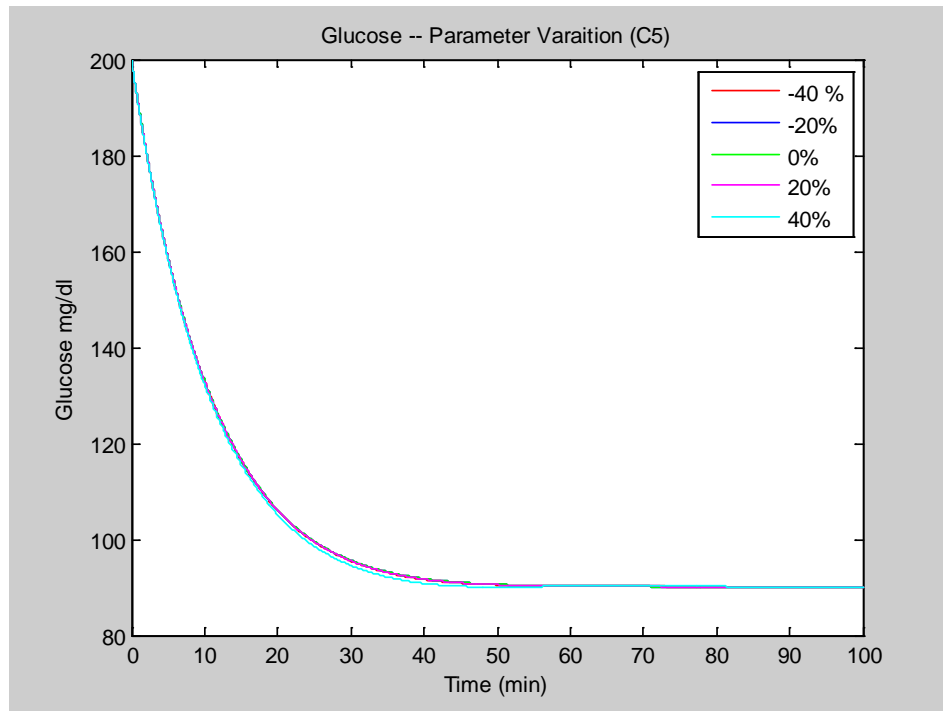


Figure 5.89: Glucose Response due to variation of parameter C5.

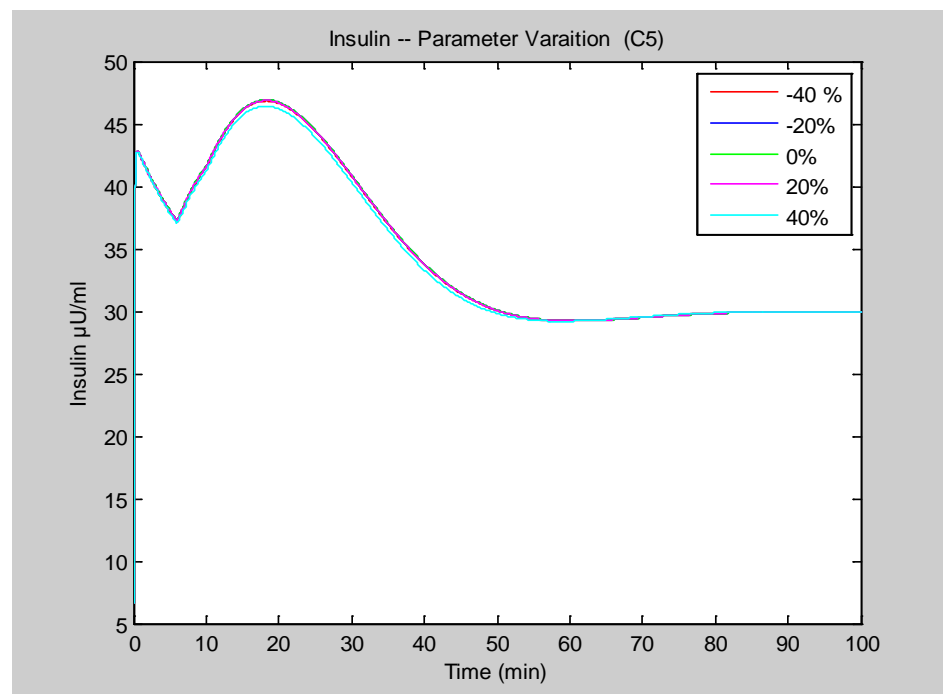
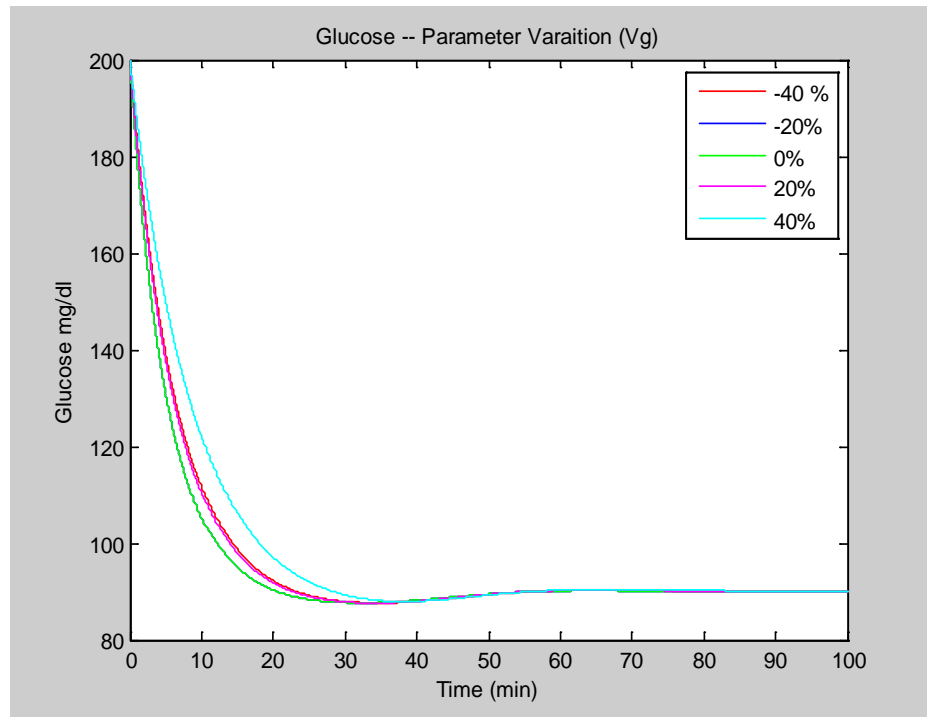


Figure 5.90: Insulin Response due to variation of parameter C5.

(c)  $V_g$ :



**Figure 5.91: Glucose Response due to variations of parameter  $V_g$ .**

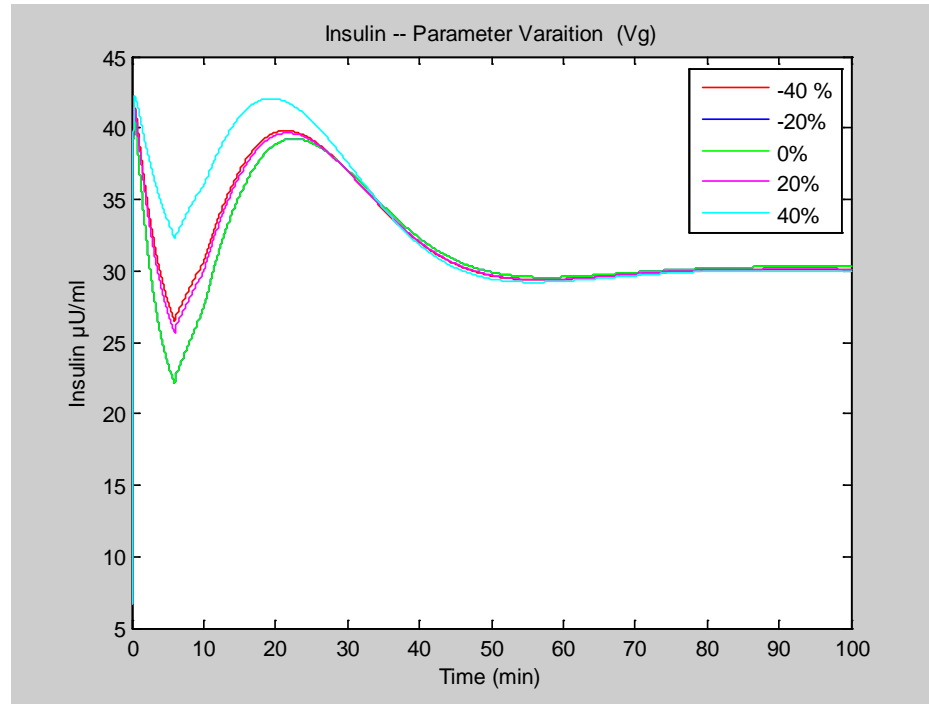


Figure 5.92: Insulin Response due to variation of parameter  $V_g$ .

(d)  $V_p$ :

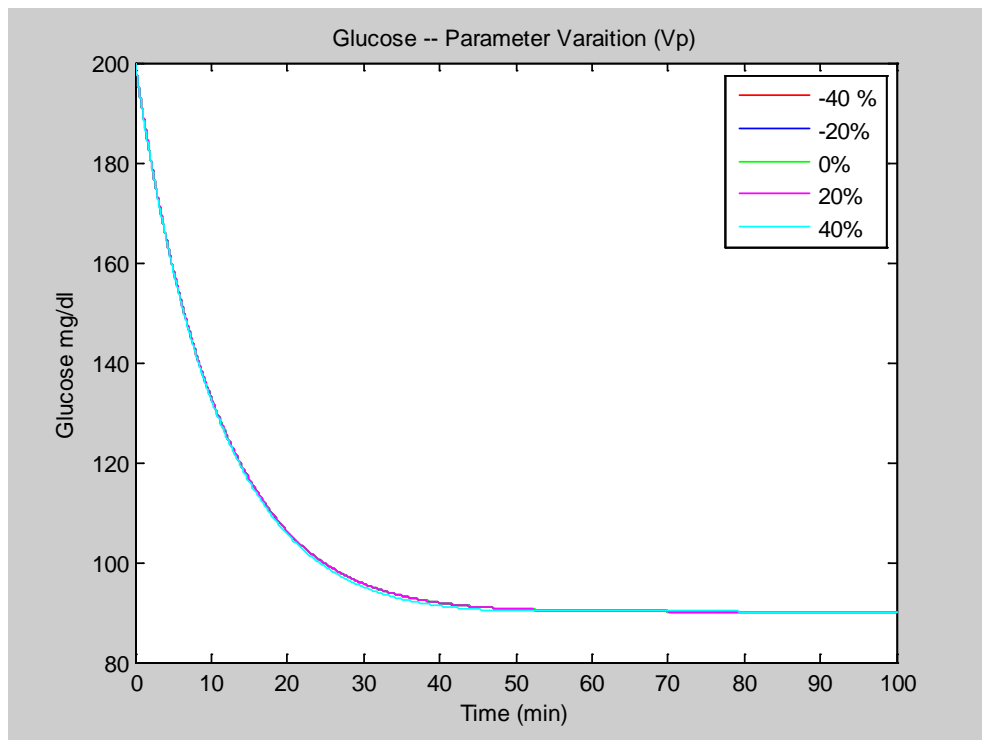


Figure 5.93: Glucose Response due to variation of parameter  $V_p$ .

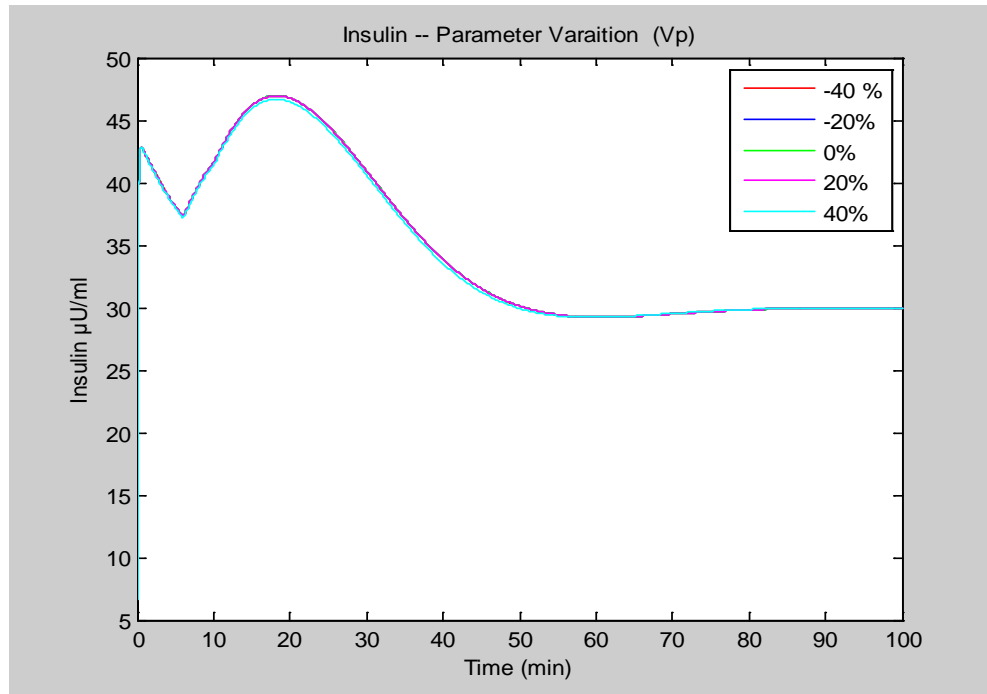


Figure 5.94: Insulin Response due to variation of parameter  $V_p$ .

(e)  $R_g$

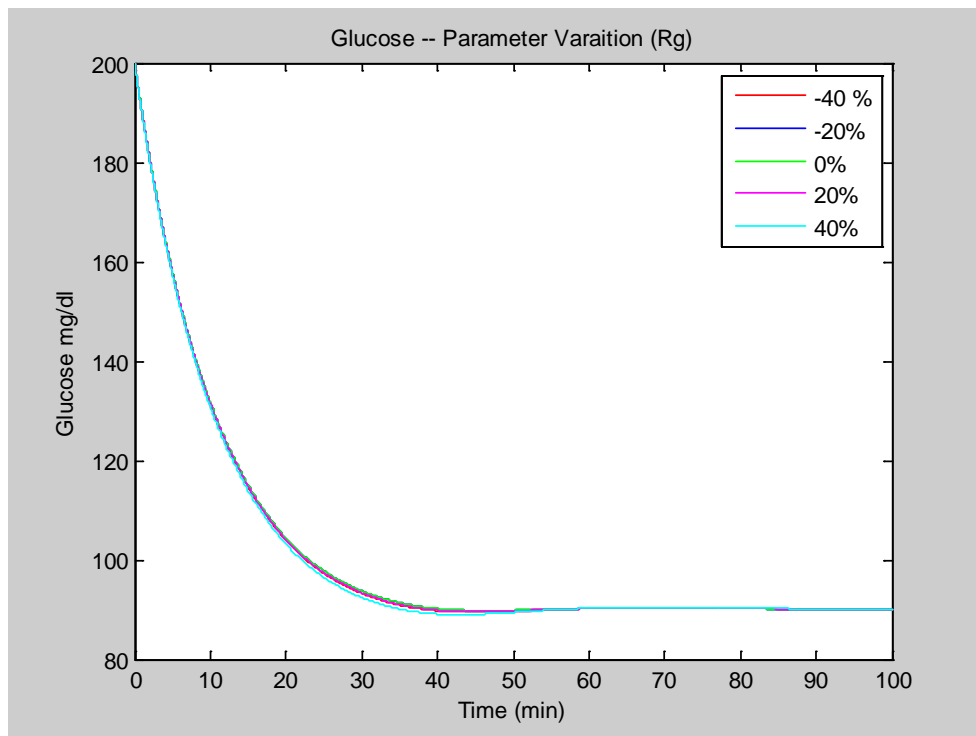


Figure 5.95: Glucose Response due to variation of parameter  $R_g$ .

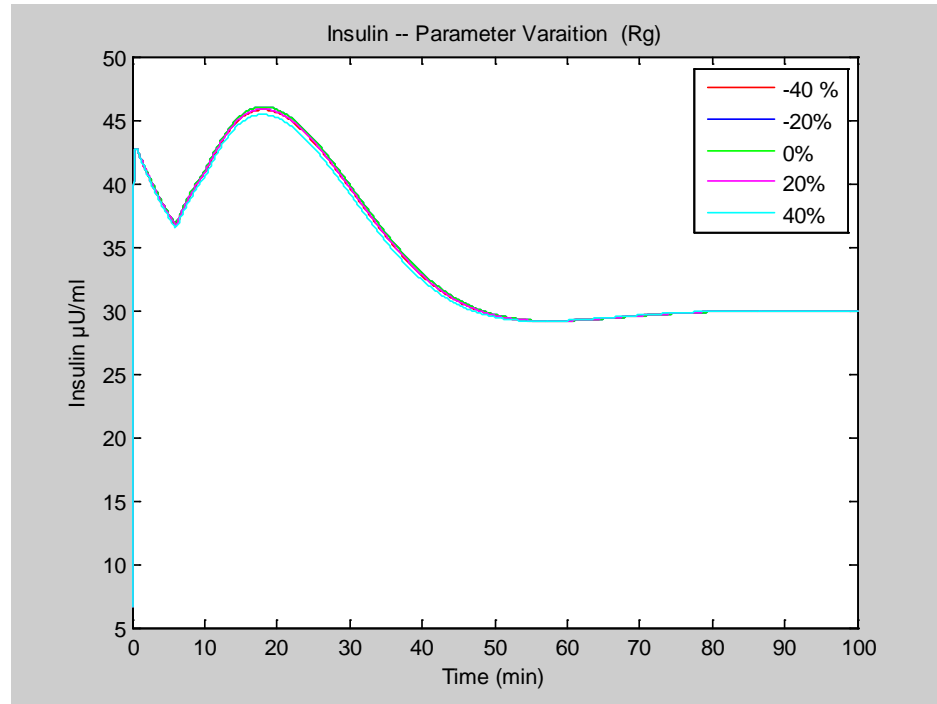


Figure 5.96: Insulin Response due to variation of parameter  $R_g$ .

(f)  $U_m$ :

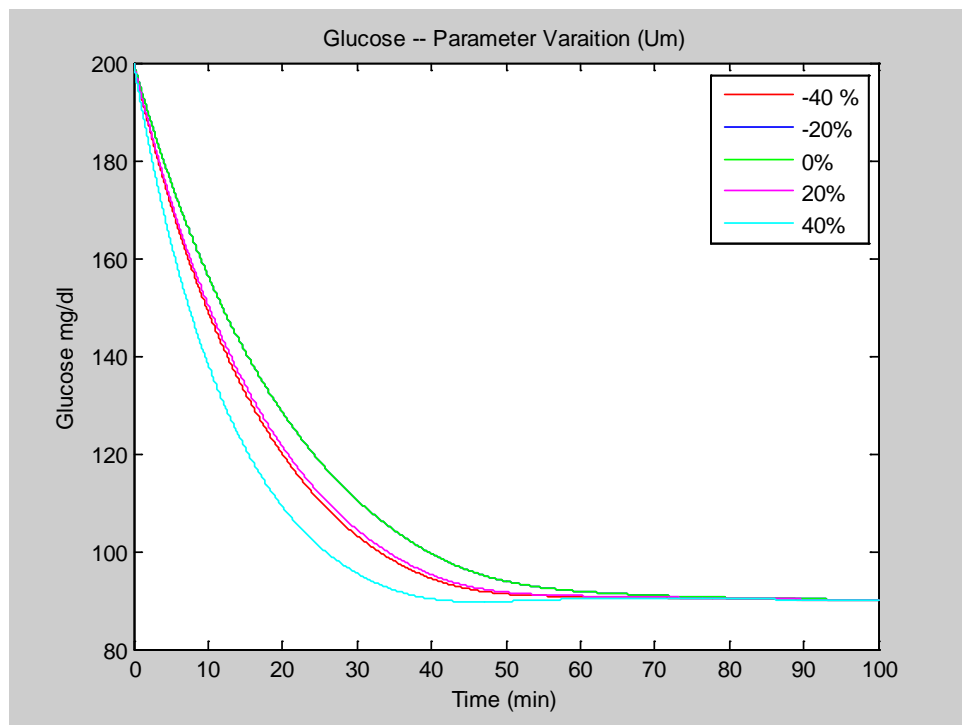
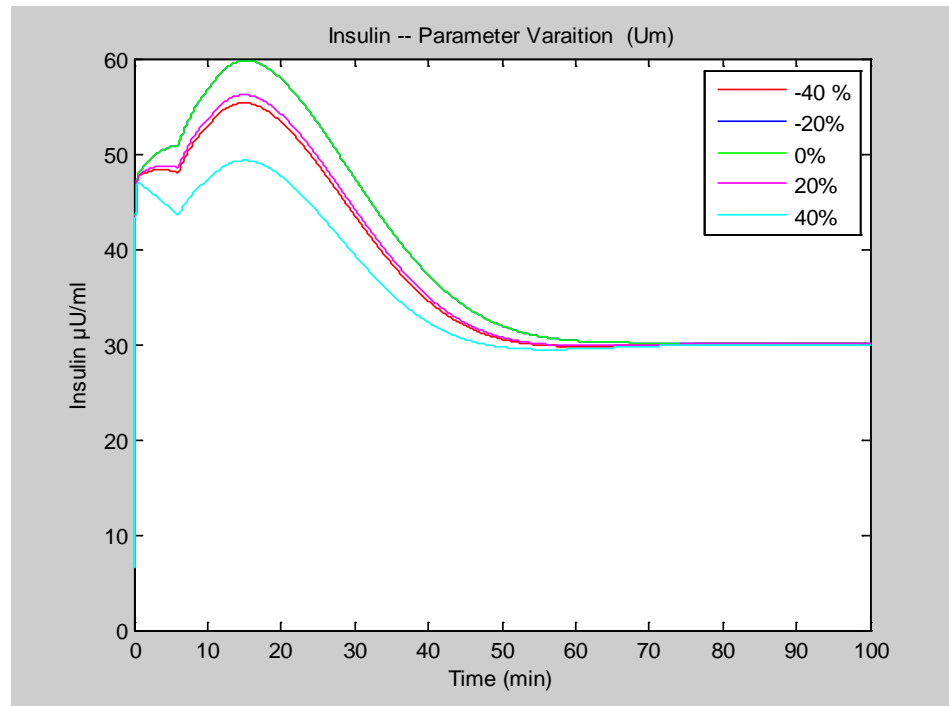


Figure 5.97: Glucose Response due to variation of parameter  $U_m$ .





**Figure 5.98: Insulin Response due to variation of parameter  $U_m$ .**

From previous simulations we can conclude that our design can sustain parameter variations.

To sum up this section, we notice that our linear estimation for the linear simulation is accurate. Also, by validating our design with the nonlinear model in the simulation, we reveal the possibility of implementing the new controller in treating diabetic patients. Also, it shows the capability to deal with main variables that are varying and affecting glucose level in the blood and responding in accurate manner to such variations. In addition, the results show that our design satisfies medical requirements which is a main point in assessing system performance.

## **Conclusion & Future work:**

Diabetes is one of the common diseases in the world. A lot of work is done in both mathematical modeling and control techniques to automate insulin delivery to the patients. Some of these techniques are implemented for special cases but none of them is fully approved for general use.

In this study, we used the two time model to represent the real process and LMI tools to drive the automated insulin delivery algorithm. We tested our work by simulating the linearized model and we validated it by using the nonlinear model. Also, we tested our design for variations in time delays and parameter variations and injection of meal disturbance. The result of our design is promising and agrees with medical requirements. So, we think that our design can be used to treat most diabetes cases.

Our design can handle parameter variations and model parameters which usually vary due to several factors. To improve this work and increase the efficiency of the controller, we recommend adaptive identification of model parameters. Moreover, we recommend cooperation between medical and control groups. This will allow for a deeper understanding of the real system by performing more analysis on the control design. Also, it will help in identifying and selecting the desired criteria such as response speed and maximum overshoot for each case.

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